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(54) Title: A NOVEL MATRIX METALLOPROTEINASE (MMP-25) EXPRESSED IN SKIN CELLS

(57) Abstract: This invention provides nucleic acids and polypeptides encoding a novel family of matrix metalloproteinases herein designated as MMP-25 and variants of the same. MMP-25 is preferentially expressed in skin cells of a mammal, particularly in breast cells and hair follicles. Expression in hair follicles is localized in the Henle layer of cells, indicating a role in hair growth. Also provided are fragments and oligonucleotides useful for identifying and isolating MMP-25-encoding nucleic acids and methods for their use, as well as antibodies that bind specifically to MMP-25 and vectors for expression of MMP-25 polypeptides. Methods of inhibiting MMP-25 activity are provided, including methods useful for inhibiting hair growth.

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Other embodiments include a nucleic acid fragment or oligonucleotide comprising at least 15 contiguous nucleotides selected from positions 1-653 of SEQ ID NO:3 or a complement thereof; and a nucleic acid fragment or oligonucleotide comprising at least 15 contiguous nucleotides selected from positions 1-741 or 1573-1841 of SEQ ID NO:5 or a complement thereof. Particular embodiments of these nucleic acid fragments or oligonucleotides include any of the above where the length is at least 18, 24, 30, 50 or greater than 50 nucleotides.

In a related aspect, the invention provides a nucleic acid fragment or oligonucleotide encoding a peptide comprised of at least 8 contiguous amino acids of the sequence according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6, with the proviso that said nucleic acid fragment is not SEQ ID NO:15 or 16. Particular embodiments of this aspect include nucleic acid fragments or oligonucleotides encoding a peptides comprised of at least 10, 15, or 20 amino acids. Still more particular embodiments include the aforementioned nucleic acid fragments wherein the encoded peptide comprises contiguous amino acids from positions 1-61, 98-111, 161-170 or 261-513 of SEQ ID NO:6.

In a similarly related aspect, the invention provides a nucleic acid fragment or oligonucleotide encoding a peptide comprised of at least 8 contiguous amino acids from positions 1-200 of SEQ ID NO:4. Particular embodiments of this aspect also include fragments or oligonucleotides comprised of at least 10, 15 or 20 amino acids. Also included within this aspect are any one of these fragments or oligonucleotides wherein the peptide comprises contiguous amino acids from positions 1-61 or 98-111 of SEQ ID NO:4. In a further related aspect, the invention provides a nucleic acid fragment or oligonucleotide encoding a peptide comprised of at least 8 contiguous amino acids from positions 1-243 of SEQ ID NO:6. Particular embodiments of this aspect also include fragments or oligonucleotides comprised of at least 10, 15 or 20 amino acids. Also included within this aspect are any one of these fragments or oligonucleotides wherein the peptide comprises contiguous amino acids positions 1-61 or 98-111, or 161-170 of SEQ ID NO:6.

The invention also includes methods of use of the aforementioned nucleic acids. In one aspect, the invention provides a method of identifying a nucleic acid encoding all or a part of a metalloproteinase, comprising the steps of: (1) hybridizing a nucleic acid sample to the nucleic acids mentioned above and (2) identifying a sequence that hybridizes thereto. In a typical practice of this method, the step of identifying includes performing a polymerase chain reaction to amplify a sequence containing the sequence that hybridizes. Thus, the invention also includes a pair of primers that specifically amplifies all or a portion of a MMP-25 nucleic acid molecule.

10 In another aspect, the invention provides vectors containing MMP-25 and related sequences. More specifically, the invention provides a recombinant nucleic acid vector containing the aforementioned MMP-25 nucleic acid sequences. In a typical embodiment, the recombinant nucleic acid vector is an expression vector containing a promoter operably linked to the MMP-25 nucleic acid sequences. In 15 another typical embodiment, the vector is selected from the group consisting of: plasmid vectors, phage vectors, herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors. In a related aspect, the invention provides for a host cell containing any of the aforementioned vectors.

The vectors provided by the present invention are useful for producing 20 MMP-25 polypeptides. Another aspect of the invention therefore includes a method of producing a MMP-25 polypeptide comprising the step of culturing a host cell comprising one of the aforementioned vectors, comprising a promoter operably linked to the MMP-25 sequence, under conditions and for a time sufficient to produce the MMP-25 polypeptide. In a preferred practice, the method further includes the step of 25 purifying the MMP-25 polypeptide.

Accordingly, the invention also provides for a polypeptide comprising an amino acid sequence selected from the group consisting of: (a) the amino acid sequence according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6; (b) an amino acid sequence having at least 50% identity to the polypeptide of (a) or (b); (c) a sequence 30 encoding a functional fragment of the polypeptide of (a) or (b); and (d) an amino acid

sequence encoded by a nucleic acid that hybridizes under conditions of normal stringency to the foregoing. More typical embodiments of these polypeptides include those having at least 50%, 60%, 70%, 80%, 90%, or 95% identity to the polypeptide according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6. In particular  
5   embodiments, identity is calculated according a MEGALIGN algorithm using a gap penalty and gap length penalty each set at a value of 10.

The polypeptides of the present invention are useful for raising antibodies thereto which are specific for MMP-25 proteins. Accordingly, another aspect of the invention is an antibody that binds to a MMP, wherein said antibody  
10   specifically binds to one of the aforementioned polypeptides. In one embodiment, the antibody is a monoclonal antibody. Typically the antibody will bind to a type 25 MMP with a higher affinity than it binds to a non type 25 MMP. The antibody is also typically, a murine or human antibody. Related aspects include an antibody selected from the group consisting of F(ab')<sub>2</sub>, F(ab)<sub>2</sub>, Fab' Fab and Fv, and a hybridoma which  
15   produces the aforementioned monoclonal antibody.

Antibodies to MMP-25 polypeptides are useful in another aspect of the invention, which is a method of identifying a type 25 MMP polypeptide comprising incubating an antibody that binds to MMP-25 polypeptide with a sample containing protein for a time sufficient to permit said antibody to bind the type 25 MMP present in  
20   the sample. In a typical practice of this method, the antibody is bound to a solid support and optionally may be labeled.

In another aspect, the invention provides for fusion proteins containing a portion of a MMP-25 polypeptide which is useful for example, in raising antibodies to particular segments of a MMP-25 polypeptide. Accordingly the invention also includes  
25   a fusion protein, comprising a first MMP-25 polypeptide segment comprised of at least eight contiguous amino acids of a MMP-25 polypeptide, fused in-frame to a second polypeptide segment comprised of a non MMP-25 polypeptide. The size of the first polypeptide segment of the fusion protein is typically at least 10, 15, or 20 amino acids in length.

In a different aspect, the nucleic acid sequences of the present invention provide for derivative nucleic acids useful for modulating or inhibiting the expression of an MMP-25 polypeptide in a cell. More specifically, the invention provides for a ribozyme that cleaves RNA encoding the aforementioned MMP-25 polypeptides. This aspect also includes a nucleic acid molecule comprising a sequence that encodes such a ribozyme and a vector comprising said nucleic acid molecule. In a related aspect, the invention provides an antisense nucleic acid molecule comprising a sequence that is antisense to a portion of the MMP-25 nucleic acids described above, a vector comprising the antisense molecule, and vectors wherein the aforementioned ribozyme or antisense nucleic acid is operably linked to a promoter. Typical embodiments of these vectors are selected from the group consisting of plasmid vectors, phage vectors, herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors. The invention also provides for a host cell comprising such a vector.

15 In yet another aspect, the invention provides a nucleic acid molecule comprising a sequence that encodes at a peptide of at least 27 amino acids in length, wherein said peptide is a consensus sequence for a Zn-binding domain of a MMP. Particular embodiments of this aspect includes SEQ ID NO:7 or SEQ ID NO:8 which are also useful for obtaining additional MMP sequences. Accordingly, the invention further provides a method of identifying a nucleic acid encoding all or a part of a MMP comprising, identifying a sequence encoded by the aforementioned consensus sequence, and cloning a sequence containing the identified sequence from a cDNA library.

In still another aspect, the MMP-25 sequences of the present invention provide for a method of inhibiting a catalytic activity of a MMP polypeptide in a cell comprising, administering an agent to the cell that inhibits a catalytic activity of the MMP, with the proviso that said agent inhibits the catalytic activity of a MMP-25 polypeptide to a greater extent than it inhibits the activity of at least one non-type 25 MMP. In a typical practice of this method, the MMP-25 polypeptide is preferentially expressed in the cell relative to the non-type 25 MMP. In one embodiment, the agent is

## DETAILED DESCRIPTION OF THE INVENTION

The following provides definitions of certain terms, and lists certain abbreviations used herein.

“Molecule” should be understood to include proteins or peptides (e.g., antibodies, recombinant binding partners, peptides with a desired binding affinity) nucleic acids (e.g., DNA, RNA, chimeric nucleic acid molecules, and nucleic acid analogues such as PNA); and organic or inorganic compounds.

“MMP-25” or “Type 25 MMP” should be understood to include any polypeptide, or nucleic acid encoding a polypeptide of the MMP family, having at least 50%, 60%, 70%, 80%, 90%, or 95% amino acid identity to any one the polypeptides provided herein as SEQ ID NO:2, 4, or 6. These polypeptides will also have less than 50% sequence identity to known MMP members designated as MMP 1-3, or 7 -22. Example sequence comparisons and identity calculations are shown in Table 1 and Figure 3.

“Non-type 25 MMP” refers to a polypeptide having less sequence identity to any of the MMPs according to SEQ ID NO:2, 4 or 6 than to another type of MMP, for example, MMPs 1-3 or 7-22. A non-type 25 MMP typically has less than 50% identity to any of the SEQ ID NO:2, 4 or 6.

“Vector” refers to an assembly that is capable of delivering a recombinant nucleic acid molecule to a cell wherein the nucleic acid molecule is maintained, either as part of an independently replicating element or as integrated into the genome of the cell. An “expression vector” is a vector that further includes transcriptional promoter elements operably linked to a recombinant nucleic acid of interest. The vector may be composed of either deoxyribonucleic acids (“DNA”), ribonucleic acids (“RNA”), or a combination of the two (e.g., a DNA-RNA chimeric). Optionally, the vector may include a polyadenylation sequence, one or more restriction sites, as well as one or more selectable markers such as neomycin phosphotransferase or hygromycin phosphotransferase. Additionally, depending on the host cell chosen and the vector employed, other genetic elements such as an origin of replication, additional nucleic acid restriction sites, enhancers, sequences conferring inducibility of

transcription, and selectable markers, may also be incorporated into the vectors described herein.

An "isolated nucleic acid molecule" is a nucleic acid molecule that is not integrated in the genomic DNA of an organism. For example, a DNA molecule that encodes a MMP-25 polypeptide that has been separated from the genomic DNA of a eukaryotic cell is an isolated DNA molecule. Another example of an isolated nucleic acid molecule is a chemically-synthesized nucleic acid molecule that is not integrated in the genome of an organism. The isolated nucleic acid molecule may be genomic DNA, cDNA, RNA, or composed at least in part of nucleic acid analogs.

10 An "isolated polypeptide" is a polypeptide that has been removed by at least one step from its original environment. For example, a naturally occurring protein is isolated if it is separated from some or all of the coexisting material in the natural system such as carbohydrate, lipid, or other proteinaceous impurities associated with the polypeptide in nature. Within certain embodiments, a particular protein preparation 15 contains an isolated polypeptide if it appears nominally as a single band on SDS-PAGE gel with Coomassie Blue staining.

A "functional fragment" of a MMP-25 polypeptide refers to a portion of a MMP-25 polypeptide that either (1) possesses a catalytic activity of a MMP-25 polypeptide, or (2) specifically binds with an anti-MMP-25 antibody.

20 "Humanized antibodies" are recombinant proteins in which murine complementarity determining regions of monoclonal antibodies have been transferred from heavy and light variable chains of the murine immunoglobulin into a human variable domain.

As used herein, an "antibody fragment" is a portion of an antibody such as F(ab')<sub>2</sub>, F(ab)<sub>2</sub>, Fab', Fab, and the like. Regardless of structure, an antibody 25 fragment binds with the same antigen that is recognized by the intact antibody. For example, an anti-MMP-25 monoclonal antibody fragment binds with an epitope of MMP-25.

The term "antibody fragment" also includes any synthetic or genetically 30 engineered protein that acts like an antibody by binding to a specific antigen to form a

corresponds to the Zn/Ca-binding domain. The conserved regions of both Zn-binding domains varied from the consensus sequences first used for the search. Therefore, use of Zn-binding domain consensus sequences are useful for identifying divergent MMPs so long as the MMP sequence contains at least one sequence having at least about 50% identity with the consensus sequences.

Despite conservation in the aforementioned polypeptide domain regions, the remainder of the MMP-25 sequences show low similarity to other MMP family members. Sequence identity was calculated as a percentage using the MEGALIGN algorithm provided with sequence alignment program DNASTAR (Madison, WI) using a Clustal method with the gap penalty and gap length penalty each set at 10. Gaps were established to maximize the number of sequence matches between the MMP-25(I) source (SEQ ID NO:5) and other MMP query sequences (SEQ ID NOs 19-36). The results are shown in Table 1.

15

Table 1

Percent Amino Acid Sequence Identity of MMP-25(I) to Other MMP Sequences

MMP	Names indicated in Figure 3	Percent Identity to MMP-25(I)
MMP-25(s)*	Contig 355 short form	99.2
MMP-1	COLL1.HUM.PRO	45.0
MMP-8	COLL2.HUM.PRO	44.5
MMP-13	COLL3.HUM.PRO	43.5
MMP-7	MATRHUM.PRO	39.7
MMP-12	METAHUM.PRO	43.2
MMP-3	STO1HUM.PRO	46.8
MMP-10	STO2HUM.PRO	46.6
MMP-11	STO3HUM.PRO	24.2
MMP-14	MTM1HUM.PRO	26.3
MMP-15	MTM2HUM.PRO	27.1
MMP-16	MTM3HUM.PRO	26.1



MMP-17P	17P	22.0
MMP-18P	18P	22.6
MMP-20P	20P	43.5
MMP-21P	21P	18.6
MMP-22P	22P	16.9
MMP-2	GELAHUM.PRO	31.6
MMP-9	GELBHUM.PRO	23.2

\*MMP-25(s) is provided herein

The highest overall sequence identity to any other known MMP is 46% to members of the stomelysin subfamily of MMPs which include MMP3, MMP10 and MMP11. A comparison of MMP-25(l) to other sequences using a different sequence comparison algorithm, namely Blastn or Blastp, also shows MMP-25 sequences to have low sequence identity with respect to other known MMP. More specifically, the greatest sequence identity obtained was 58% to a *Gallus gallus* MMP sequence. These programs were run using default settings. However these programs do not return an identity score that evaluates the whole of the MMP-25 sequence, but only evaluates those portions of MMP-25 sequences where some level of identity to the comparison sequence can be found. Typically, there is no significant identity to other MMP sequences in the region corresponding to positions 481-510 of SEQ ID NO:6 (which corresponds to positions 438-470 of SEQ ID NO:4). Accordingly, the overall sequence identity of MMP-25 to other known sequences is less than 50% when the whole of the MMP-25 sequence is compared to a other MMP sequences using BLAST programs as well as MEGALIGN.

Figure 3 illustrates patterns of sequence identity between the MMP-25 sequences of the present invention in comparison to eighteen other known MMP sequences. The comparison indicates regions where sequence identity is high, which include the aforementioned domains common amongst MMP proteins which are also depicted Figure 3. In addition, Figure 3 indicates that there are regions of low identity between MMP-25 and other MMP sequences. Regions of low identity are particularly useful for identifying MMP-25 family members by hybridization or antibody

MMP-25 antibody. For example, the MMP-25 polypeptide encoded by the 833 nucleotide fragment (SEQ ID NO:2) is a functional fragment of the larger MMP-25 disclosed above as SEQ ID NO 6.

#### Fragments and oligonucleotides

5 Also provided herein are nucleic acid fragments or oligonucleotides useful as probes and primers for identifying or obtaining MMP-25 sequences. More specifically, a nucleic acid fragment or oligonucleotide should comprise at least 15 contiguous nucleotides of SEQ ID NO:1 or SEQ ID NO:3, or SEQ ID NO:5 with the proviso that said nucleic acid fragment is not SEQ ID NO:15 or 16. More particular  
10 embodiments include fragments or oligonucleotides such as positions 1-653 of SEQ ID NO:3 or 1-741 or 1573-1841 of SEQ ID NO:5. Particular embodiments of these nucleic acid fragments or oligonucleotides include any of the above where the length is at least 18, 24, 30, 50 or greater than 50 nucleotides. Complements of the above sequences are also included.

15 Another embodiment of nucleic acid fragments or oligonucleotides of this invention include those that encode a peptide epitope that can be detected, for example, by the ability to specifically bind to a MMP-25 antibody or which can be used to elicit an immune response in an animal. Useful peptide epitopes are those capable of eliciting antibodies that specifically bind to the peptide or polypeptide comprised of the  
20 same, or that are capable of eliciting a T-cell response. Peptide sequences of 8 or more amino acids are useful in this regard since it is generally understood by those skilled in the art that 8 amino acids is the lower size limit for a peptide to interact with the major histocompatibility complex (MHC). More preferred embodiments include nucleic acid fragments or oligonucleotides encoding at least 10, 15 or 20 amino acids.

25 Therefore, the present invention provides for nucleic acid fragments or oligonucleotides encoding a peptide comprised of at least 8 contiguous amino acids of the sequence according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6, with the proviso that said nucleic acid fragment is not SEQ ID NO:15 or 16. Particular embodiments of this aspect include nucleic acid fragments or oligonucleotides encoding

a peptide comprised of at least 10, 15, or 20 amino acids. Still more particular embodiments include nucleic acid fragments wherein the encoded peptide comprises sequences particularly distinctive of MMP-25 polypeptides. These include sequence such as those encoding peptides from positions 1-243 of SEQ ID NO:6. Other preferred sequences that are distinctive of MMP-25 include those encoding peptides from positions 1-61, 98-111, 161-170 or 261-513 of SEQ ID NO:6. Also included in this regard are nucleic acids encoding at least 8, 10, 15 or 20 amino acids from positions 1-200 of SEQ ID NO:4, with preferred fragments or oligonucleotides encoding a peptide from positions 1-61 or 98-111 of SEQ ID NO:4.

#### 10 Methods of use of nucleic acids, fragments and oligonucleotides

The aforementioned nucleic acids fragments and oligonucleotides are useful for the identification or isolation of MMP-25 nucleic acids, polypeptides and variants thereof. Typically, the nucleic acid fragments are used for probes for hybridization to sample sequences or as primers for PCR reactions. Thus, the invention provides for methods of identifying a nucleic acid encoding all or a part of a metalloproteinase, comprising the steps of: (1) hybridizing a nucleic acid sample to the nucleic acids mentioned above and (2) identifying a sequence that hybridizes thereto. In a typical practice of this method, the step of identifying includes performing a polymerase chain reaction to amplify a sequence containing the sequence that hybridizes. Thus the invention also includes at least one pair of primers that specifically amplifies all or a portion of a MMP-25 nucleic acid molecule.

In addition, as discussed above, the present invention includes consensus sequences for a Zn or Zn/Ca-binding domain of MMPs. The consensus sequences used are unique, and permit identification and isolation of MMP sequences having at least 50% identity to the consensus sequences. Therefore, another aspect of the present invention provides a nucleic acid comprising a sequence that encodes a peptide of at least 27 amino acids in length, wherein said peptide is a consensus sequence for a Zn-binding domain of a MMP. Particular embodiments of this aspect include SEQ ID NO:7 or SEQ ID NO:8. In a related aspect, the invention provides a general method of

identifying a nucleic acid encoding all or a part of a MMP that includes the steps of identifying a sequence encoded by the aforementioned consensus sequences, and cloning a sequence containing the identified sequence from a cDNA library.

#### Identification and Isolation of MMP-25 nucleic acids

5 DNA molecules encoding a gene can be obtained by screening a human cDNA or genomic library using polynucleotide probes based upon the aforementioned MMP-25 sequences, fragments and oligonucleotides.

For example, the first step in the preparation of a cDNA library is to isolate RNA using methods well-known to those of skill in the art. In general, RNA isolation techniques provide a method for breaking cells, a means of inhibiting RNase-directed degradation of RNA, and a method of separating RNA from DNA, protein, and polysaccharide contaminants. For example, total RNA can be isolated by freezing tissue in liquid nitrogen, grinding the frozen tissue with a mortar and pestle to lyse the cells, extracting the ground tissue with a solution of phenol/chloroform to remove proteins, and separating RNA from the remaining impurities by selective precipitation with lithium chloride (see, for example, Ausubel et al. (eds.), *Short Protocols in Molecular Biology*, 3rd Edition, pages 4-1 to 4-6 (John Wiley & Sons 1995) ["Ausubel (1995)"]; Wu et al., *Methods in Gene Biotechnology*, pages 33-41 (CRC Press, Inc. 1997) ["Wu (1997)"]).

Alternatively, total RNA can be isolated by extracting ground tissue with guanidinium isothiocyanate, extracting with organic solvents, and separating RNA from contaminants using differential centrifugation (see, for example, Ausubel (1995) at pages 4-1 to 4-6; Wu (1997) at pages 33-41).

In order to construct a cDNA library, poly(A)<sup>+</sup> RNA is isolated from a total RNA preparation. Poly(A)<sup>+</sup> RNA can be isolated from total RNA by using the standard technique of oligo(dT)-cellulose chromatography (see, for example, Ausubel (1995) at pages 4-11 to 4-12).

Double-stranded cDNA molecules are synthesized from poly(A)<sup>+</sup> RNA using techniques well known to those in the art. (see, for example, Wu (1997) at pages 41-46). Commercially available kits can be used to synthesize double-stranded cDNA

molecules. For example, such kits are available from Life Technologies, Inc. (Gaithersburg, Maryland), Clontech Laboratories, Inc. (Palo Alto, California), Promega Corporation (Madison, Wisconsin) and Stratagene Cloning Systems (La Jolla, California).

5 The basic approach for obtaining MMP-25 cDNA clones can be modified by constructing a subtracted cDNA library which is enriched in MMP cDNA molecules. Techniques for constructing subtracted libraries are well-known to those of skill in the art (see, for example, Sargent, "Isolation of Differentially Expressed Genes," in *Meth. Enzymol.* 152:423, 1987, and Wu et al. (eds.), "Construction and Screening of Subtracted and Complete Expression cDNA Libraries," in *Methods in Gene Biotechnology*, pages 29-10 65 (CRC Press, Inc. 1997)).

Various cloning vectors are appropriate for the construction of a cDNA library. For example, a cDNA library can be prepared in a vector derived from bacteriophage, such as a  $\lambda$ gt10 vector (see, for example, Huynh et al., "Constructing and Screening cDNA Libraries in  $\lambda$ gt10 and  $\lambda$ gt11," in *DNA Cloning: A Practical Approach Vol. I*, Glover (ed.), page 49 (IRL Press, 1985); Wu (1997) at pages 47-52).

Alternatively, double-stranded cDNA molecules can be inserted into a plasmid vector, such as a pBluescript vector (Stratagene Cloning Systems; La Jolla, California), a LambdaGEM-4 (Promega Corp.; Madison, Wisconsin) or other 20 commercially available vectors. Suitable cloning vectors also can be obtained from the American Type Culture Collection (Rockville, Maryland).

In order to amplify the cloned cDNA molecules, the cDNA library is inserted into a prokaryotic host, using standard techniques. For example, a cDNA library can be introduced into competent *E. coli* DH5 cells, which can be obtained from Life 25 Technologies, Inc. (Gaithersburg, Maryland).

A human genomic DNA library can be prepared by means well-known in the art (see, for example, Ausubel (1995) at pages 5-1 to 5-6; Wu (1997) at pages 307-327). Genomic DNA can be isolated by lysing tissue with the detergent Sarkosyl, digesting the lysate with proteinase K, clearing insoluble debris from the lysate by

centrifugation, precipitating nucleic acid from the lysate using isopropanol, and purifying resuspended DNA on a cesium chloride density gradient.

DNA fragments that are suitable for the production of a genomic library can be obtained by the random shearing of genomic DNA or by the partial digestion of genomic DNA with restriction endonucleases. Genomic DNA fragments can be inserted into a vector, such as a bacteriophage or cosmid vector, in accordance with conventional techniques, such as the use of restriction enzyme digestion to provide appropriate termini, the use of alkaline phosphatase treatment to avoid undesirable joining of DNA molecules, and ligation with appropriate ligases. Techniques for such manipulation are well-known in the art (see, for example, Ausubel (1995) at pages 5-1 to 5-6; Wu (1997) at pages 307-327).

Nucleic acid molecules that encode a MMP-25 gene can also be obtained using the polymerase chain reaction (PCR) with oligonucleotide primers having nucleotide sequences that are based upon the nucleotide sequences of the human MMP-25 gene, as described herein. General methods for screening libraries with PCR are provided by, for example, Yu et al., "Use of the Polymerase Chain Reaction to Screen Phage Libraries," in *Methods in Molecular Biology, Vol. 15:PCR Protocols:Current Methods and Applications*, White (ed.), pages 211-215 (Humana Press, Inc. 1993). Techniques for using PCR to isolate related genes are described by, for example, Preston, "Use of Degenerate Oligonucleotide Primers and the Polymerase Chain Reaction to Clone Gene Family Members," in *Methods in Molecular Biology, Vol. 15:PCR Protocols:Current Methods and Applications*, White (ed.), pages 317-337 (Humana Press, Inc. 1993). Examples 1 and 2 illustrate one approach to obtaining MMP-25 nucleic acids using RT-PCR.

Alternatively, human genomic libraries can be obtained from commercial sources such as Research Genetics (Huntsville, AL) and the American Type Culture Collection (Rockville, Maryland).

A library containing cDNA or genomic clones can be screened with one or more polynucleotide probes based upon SEQ ID NO:1, 3, or 5 using standard methods (see, for example, Ausubel (1995) at pages 6-1 to 6-11).

Anti-MMP-25 antibodies, produced as described below, can also be used to isolate DNA sequences that encode MMP-25 genes from cDNA libraries. For example, the antibodies can be used to screen  $\lambda$ gt11 expression libraries, or the antibodies can be used for immunoscreening following hybrid selection and translation (see, for example, Ausubel (1995) at pages 6-12 to 6-16; Margolis et al., "Screening  $\lambda$  expression libraries with antibody and protein probes," in *DNA Cloning 2: Expression Systems, 2nd Edition*, Glover et al. (eds.), pages 1-14 (Oxford University Press 1995)).

The sequence of a MMP-25 cDNA or MMP-25 genomic fragment can be determined using standard methods. The identification of genomic fragments containing a MMP-25 promoter or regulatory element can be achieved using well-established techniques, such as deletion analysis (Ausubel (1995)).

A MMP-25 gene can also be obtained by synthesizing DNA molecules using mutually priming long oligonucleotides and the nucleotide sequences described herein (Ausubel (1995) at pages 8-8 to 8-9). Established techniques using the polymerase chain reaction provide the ability to synthesize DNA molecules at least two kilobases in length (Adang et al., *Plant Molec. Biol.* 21:1131, 1993; Bambot et al., *PCR Methods and Applications* 2:266, 1993; Dillon et al., "Use of the Polymerase Chain Reaction for the Rapid Construction of Synthetic Genes," in *Methods in Molecular Biology, Vol. 15: PCR Protocols: Current Methods and Applications*, White (ed.), pages 263-268 (Humana Press, Inc. 1993); Holowachuk et al., *PCR Methods Appl.* 4:299, 1995).

#### Production of Variants

Nucleic acid molecules encoding variant MMP-25 nucleic acids can be produced by screening various cDNA or genomic libraries with polynucleotide probes having nucleotide sequences based upon SEQ ID NO:1, 3 or 5 and the fragments or oligonucleotides derived therefrom described above. MMP-25 nucleic acids and variants can also be constructed synthetically. For example, a nucleic acid molecule can be obtained that encodes a polypeptide having a conservative amino acid change, compared with the amino acid sequence of SEQ ID NO:2, 4, or 6. That is, variants can

performed in 0.5xSSC (1xSSC = 150 mM sodium chloride, 15 mM trisodium citrate) or in 0.5xSSPE at 55-60°C. Stringent hybridization conditions typically hybridize 1-2x SSPE (or equivalent salt concentration) overnight at 48-65°C, with or without a strand denaturant such as 50% formamide, followed by a wash in 0.1-0.2% SSC at about 65°C.

## 5 Vectors

The invention provides for recombinant nucleic acid vectors comprising the aforementioned MMP-25 nucleic acids and related sequences. In a typical embodiment, the vector is an expression vector containing a promoter operably linked to the MMP-25 nucleic acid sequence for use in expressing a MMP-25 RNA,  
10 polypeptide or fragment thereof. The vector may be selected from any type of vector depending on intended use and host cell type. These include plasmid vectors, phage vectors, herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors.

To express a MMP-25 gene, a nucleic acid molecule encoding the  
15 polypeptide must be operably linked to regulatory sequences that control transcriptional expression in an expression vector and then introduced into a host cell. In addition to transcriptional regulatory sequences, such as promoters and enhancers, expression vectors can include translational regulatory sequences and a marker gene which is suitable for selection of cells that carry the expression vector.

20 Expression vectors that are suitable for production of a foreign protein in eukaryotic cells typically contain (1) prokaryotic DNA elements coding for a bacterial replication origin and an antibiotic resistance marker to provide for the growth and selection of the expression vector in a bacterial host; (2) eukaryotic DNA elements that control initiation of transcription, such as a promoter; and (3) DNA elements that control  
25 the processing of transcripts, such as a transcription termination/polyadenylation sequence.

MMP-25 nucleic acids of the present invention are preferably expressed in mammalian cells. Examples of mammalian host cells include African green monkey kidney cells (Vero; ATCC CRL 1587), human embryonic kidney cells (293-HEK; ATCC CRL 1573), baby hamster kidney cells (BHK-21; ATCC CRL 8544), canine kidney cells



(MDCK; ATCC CCL 34), Chinese hamster ovary cells (CHO-K1; ATCC CCL61), rat pituitary cells (GH1; ATCC CCL82), HeLa S3 cells (ATCC CCL2.2), rat hepatoma cells (H-4-II-E; ATCC CRL 1548) SV40-transformed monkey kidney cells (COS-1; ATCC CRL 1650) and murine embryonic cells (NIH-3T3; ATCC CRL 1658).

5 For a mammalian host, the transcriptional and translational regulatory signals may be derived from viral sources, such as adenovirus, bovine papilloma virus, simian virus, or the like, in which the regulatory signals are associated with a particular gene which has a high level of expression. Suitable transcriptional and translational regulatory sequences also can be obtained from mammalian genes, such as actin, collagen, 10 myosin, and metallothionein genes.

Transcriptional regulatory sequences include a promoter region sufficient to direct the initiation of RNA synthesis. Suitable eukaryotic promoters include, for example, the promoter of the mouse metallothionein I gene (Hamer et al., *J. Molec. Appl. Genet.* 1:273, 1982), the TK promoter of Herpes virus (McKnight, *Cell* 31:355, 1982), the 15 SV40 early promoter (Benioist et al., *Nature* 290:304, 1981), the Rous sarcoma virus promoter (Gorman et al., *Proc. Nat'l Acad. Sci. USA* 79:6777, 1982), the cytomegalovirus promoter (Foecking et al., *Gene* 45:101, 1980), and the mouse mammary tumor virus promoter (see, generally, Etcheverry, "Expression of Engineered Proteins in Mammalian Cell Culture," in *Protein Engineering: Principles and Practice*, Cleland et al. (eds.), pages 20 163-181 (John Wiley & Sons, Inc. 1996)).

Alternatively, a prokaryotic promoter, such as the bacteriophage T3 RNA polymerase promoter, can be used to control MMP-25 gene expression in mammalian cells if the prokaryotic promoter is regulated by a eukaryotic promoter (Zhou et al., *Mol. Cell. Biol.* 10:4529, 1990; Kaufman et al., *Nucl. Acids Res.* 19:4485, 1991).

25 MMP-25 genes may also be expressed in bacterial, yeast, insect, or plant cells. Suitable promoters that can be used to express MMP-25 polypeptides in a prokaryotic host are well-known to those of skill in the art and include promoters capable of recognizing the T4, T3, Sp6 and T7 polymerases, the P<sub>R</sub> and P<sub>L</sub> promoters of bacteriophage lambda, the *trp*, *recA*, heat shock, *lacUV5*, *tac*, *lpp-lacSpr*, *phoA*, and 30 *lacZ* promoters of *E. coli*, promoters of *B. subtilis*, the promoters of the bacteriophages

of *Bacillus*, *Streptomyces* promoters, the *int* promoter of bacteriophage lambda, the *bla* promoter of pBR322, and the CAT promoter of the chloramphenicol acetyl transferase gene. See Glick, *J. Ind. Microbiol.* 1:277, 1987, Watson et al., *Molecular Biology of the Gene*, 4th Ed. (Benjamin Cummins 1987), and by Ausubel et al. (1995).

5 Preferred prokaryotic hosts include *E. coli* and *B. subtilis*. Suitable strains of *E. coli* include BL21(DE3), BL21(DE3)pLysS, BL21(DE3)pLysE, DH1, DH4I, DH5, DH5I, DH5IF', DH5IMCR, DH10B, DH10B/p3, DH11S, C600, HB101, JM101, JM105, JM109, JM110, K38, RR1, Y1088, Y1089, CSH18, ER1451, and ER1647 (see, for example, Brown (Ed.), *Molecular Biology Labfax* (Academic Press  
10 1991)). Suitable strains of *Bacillus subtilis* include BR151, YB886, MI119, MI120, and B170 (see, for example, Hardy, "Bacillus Cloning Methods," in *DNA Cloning: A Practical Approach*, Glover (Ed.) (IRL Press 1985)).

Methods for expressing proteins in prokaryotic hosts are well-known to those of skill in the art (see, for example, Williams et al., "Expression of foreign  
15 proteins in *E. coli* using plasmid vectors and purification of specific polyclonal antibodies," in *DNA Cloning 2: Expression Systems*, 2nd Edition, Glover et al. (eds.), page 15 (Oxford University Press 1995); Ward et al., "Genetic Manipulation and Expression of Antibodies," in *Monoclonal Antibodies: Principles and Applications*, page 137 (Wiley-Liss, Inc. 1995); and Georgiou, "Expression of Proteins in Bacteria,"  
20 in *Protein Engineering: Principles and Practice*, Cleland et al. (eds.), page 101 (John Wiley & Sons, Inc. 1996)).

The baculovirus system provides an efficient means to introduce cloned MMP-25 genes into insect cells. Suitable expression vectors are based upon the *Autographa californica* multiple nuclear polyhedrosis virus (AcMNPV), and contain  
25 well-known promoters such as *Drosophila* heat shock protein (hsp) 70 promoter, *Autographa californica* nuclear polyhedrosis virus immediate-early gene promoter (*ie-1*) and the delayed early 39K promoter, baculovirus p10 promoter, and the *Drosophila* metallothionein promoter. Suitable insect host cells include cell lines derived from IPLB-Sf-21, a *Spodoptera frugiperda* pupal ovarian cell line, such as Sf9 (ATCC CRL  
30 1711), Sf21AE, and Sf21 (Invitrogen Corporation; San Diego, CA), as well as

*Drosophila* Schneider-2 cells. Established techniques for producing recombinant proteins in baculovirus systems are provided by Bailey et al., "Manipulation of Baculovirus Vectors," in *Methods in Molecular Biology, Volume 7: Gene Transfer and Expression Protocols*, Murray (ed.), pages 147-168 (The Humana Press, Inc. 1991), by Patel et al., "The baculovirus expression system," in *DNA Cloning 2: Expression Systems, 2nd Edition*, Glover et al. (eds.), pages 205-244 (Oxford University Press 1995), by Ausubel (1995) at pages 16-37 to 16-57, by Richardson (ed.), *Baculovirus Expression Protocols* (The Humana Press, Inc. 1995), and by Lucknow, "Insect Cell Expression Technology," in *Protein Engineering: Principles and Practice*, Cleland et al. (eds.), pages 183-218 (John Wiley & Sons, Inc. 1996).

Promoters for expression in yeast include promoters from *GAL1* (galactose), *PGK* (phosphoglycerate kinase), *ADH* (alcohol dehydrogenase), *AOX1* (alcohol oxidase), *HIS4* (histidinol dehydrogenase), and the like. Many yeast cloning vectors have been designed and are readily available. These vectors include YIp-based vectors, such as YIp5, YRp vectors, such as YRp17, YEp vectors such as YEp13 and YCp vectors, such as YCp19. One skilled in the art will appreciate that there are a wide variety of suitable vectors for expression in yeast cells.

Expression vectors can also be introduced into plant protoplasts, intact plant tissues, or isolated plant cells. General methods of culturing plant tissues are provided, for example, by Miki et al., "Procedures for Introducing Foreign DNA into Plants," in *Methods in Plant Molecular Biology and Biotechnology*, Glick et al. (eds.), pages 67-88 (CRC Press, 1993).

An expression vector can be introduced into host cells using a variety of standard techniques including calcium phosphate transfection, liposome-mediated transfection, microprojectile-mediated delivery, electroporation, and the like. Preferably, the transfected cells are selected and propagated to provide recombinant host cells that comprise the expression vector stably integrated in the host cell genome. Techniques for introducing vectors into eukaryotic cells and techniques for selecting such stable transformants using a dominant selectable marker are described, for example, by Ausubel (1995) and by Murray (ed.), *Gene Transfer and Expression Protocols* (Humana Press

example within inclusion bodies in prokaryotic hosts. When engineered for export, a supernatant from a culture of the host cell can be used to isolate the exported MMP-25 polypeptide. Typically, the MMP-25 polypeptides used for export in a mammalian cell will include the same export signal that naturally occur with the MMP-25 such as the leader peptide as indicated in Figures 2 and 3. Alternatively, export signals such as leader peptide domains from different exported proteins can be fused to a MMP-25 polypeptide to provide for export in particular cell types.

When expressed in prokaryotic cells, MMP-25 may be isolated from inclusion bodies by a variety of purification procedures. For example, a fraction containing inclusion bodies can be separated from a soluble fraction of disrupted host cells by centrifugation or filtration and the MMP-25-polypeptide can be extracted therefrom using detergents. Optional further purification steps may include binding a sample to MMP-25 antibody bound to a suitable support. In addition, anion or cation exchange resins, gel filtration or affinity, hydrophobic or reverse phase chromatography may be employed in order to purify the protein.

In another alternative, the MMP-25 polypeptide can be isolated from an animal cell such as breast or skin cells in which it is naturally expressed. MMP-25 polypeptides can be purified by any of one or more of the steps common used to purify metalloproteinases generally. In addition or alternatively, the MMP-25 can be excised from a polyacrylamide gel after electrophoresis and identification of the appropriate 54 KD band on the gel as described in Example 5.

#### Fusion Proteins

The discussion above of isolation of proteins is equally applicable to the isolation of fusion proteins containing a portion of a MMP-25 polypeptide fused to another protein. Fusion proteins are useful for several purposes, including the combining of two or more catalytic functions from separate polypeptide sources, and for raising antibodies to epitopes. For raising antibodies to epitopes, the fusion protein typically contains a peptide epitope of a MMP-25 of at least 8, 10, 15 or 20 amino acids fused to a protein that enhances an immune response to the epitope. A typical protein

for this purpose is KLH. Therefore, another aspect of the present invention provides a non-naturally occurring fusion protein, comprising a first MMP-25 polypeptide segment comprised of at least 8 contiguous amino acids of a MMP-25 polypeptide or variant described above, fused in-frame to a second polypeptide segment. The second polypeptide segment may comprise another portion of the MMP-25 polypeptide that is not naturally adjacent to the first segment, or comprise sequences from a non MMP-25 polypeptide.

#### Manipulation, Mutation and Expression of Polypeptides

Although various genes (or portions thereof) have been provided herein, it should be understood that within the context of the present invention, reference to one or more of these genes includes derivatives of the genes that are substantially similar to the genes (and, where appropriate, the proteins (including peptides and polypeptides) that are encoded by the genes and their derivatives). As used herein, a nucleotide sequence is deemed to be "substantially similar" if: (a) the nucleotide sequence is derived from the coding region of the above-described genes and includes, for example, portions of the sequence or allelic variations of the sequences discussed above, or alternatively, encodes a molecule which inhibits the binding of MMP-25 to a member of the MMP-25 family, (b) the nucleotide sequence is capable of hybridization to nucleotide sequences of the present invention under moderate, or high stringency as mentioned above. (also see Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, NY, 1989); or (c) the DNA sequences are degenerate as a result of the genetic code in relation to the DNA sequences defined in (a) or (b). Further, the nucleic acid molecule disclosed herein includes both complementary and non-complementary sequences, provided the sequences otherwise meet the criteria set forth herein.

The structure of the proteins encoded by the nucleic acid molecules described herein may be predicted from the primary translation products using the hydrophobicity plot function of, for example, P/C Gene or Intelligenetics Suite

including bacterial, mammalian, yeast or other fungi, viral, insect, or plant cells as described above.

Techniques for transforming fungi are well known in the literature, and have been described, for instance, by Beggs (*ibid.*), Hinnen et al. (*Proc. Natl. Acad. Sci. USA* 75:1929-1933, 1978), Yelton et al. (*Proc. Natl. Acad. Sci. USA* 81:1740-1747, 1984), and Russell (*Nature* 301:167-169, 1983). The genotype of the host cell may contain a genetic defect that is complemented by the selectable marker present on the expression vector. Choice of a particular host and selectable marker is well within the level of ordinary skill in the art.

Protocols for the transformation of yeast are also well known to those of ordinary skill in the art. For example, transformation may be readily accomplished either by preparation of spheroplasts of yeast with DNA (*see* Hinnen et al., *PNAS USA* 75:1929, 1978) or by treatment with alkaline salts such as LiCl (*see* Itoh et al., *J. Bacteriology* 153:163, 1983). Transformation of fungi may also be carried out using polyethylene glycol as described by Cullen et al. (*Bio/Technology* 5:369, 1987).

Viral vectors include those which comprise a promoter that directs the expression of an isolated nucleic acid molecule that encodes a desired protein as described above. A wide variety of promoters may be utilized within the context of the present invention, including for example, promoters such as MoMLV LTR, RSV LTR, Friend MuLV LTR, adenoviral promoter (Ohno et al., *Science* 265:781-784, 1994), neomycin phosphotransferase promoter/enhancer, late parvovirus promoter (Koering et al., *Hum. Gene Therap.* 5:457-463, 1994), Herpes TK promoter, SV40 promoter, metallothionein IIa gene enhancer/promoter, cytomegalovirus immediate early promoter, and the cytomegalovirus immediate late promoter. Within particularly preferred embodiments of the invention, the promoter is a tissue-specific promoter (*see e.g.*, WO 91/02805; EP 0,415,731; and WO 90/07936). Representative examples of suitable tissue specific promoters include neural specific enolase promoter, platelet derived growth factor beta promoter, bone morphogenic protein promoter, human alpha1-chimaerin promoter, synapsin I promoter and synapsin II promoter. In addition to the above-noted promoters, other viral-specific promoters (*e.g.*, retroviral promoters

(including those noted above, as well as others such as HIV promoters), hepatitis, herpes (e.g., EBV), and bacterial, fungal or parasitic (e.g., malarial) -specific promoters may be utilized in order to target a specific cell or tissue which is infected with a virus, bacteria, fungus or parasite.

5 Mammalian cells suitable for carrying out the present invention include, among others COS, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, and human or mammalian bone marrow stroma. Mammalian expression vectors for use in carrying out the present invention will include a promoter capable of directing the transcription of a cloned gene or cDNA. Preferred promoters include viral promoters and cellular promoters. Bone specific promoters include the bone sialo-protein and the promoter for osteocalcin. Viral promoters include the cytomegalovirus immediate early promoter (Boshart et al., *Cell* 41:521-530, 1985), cytomegalovirus immediate late promoter, SV40 promoter (Subramani et al., *Mol. Cell. Biol.* 1:854-864, 1981), MMTV LTR, RSV LTR, metallothionein-1, adenovirus E1a. Cellular promoters include the mouse metallothionein-1 promoter (Palmiter et al., U.S. Patent No. 4,579,821), a mouse  $V_K$  promoter (Bergman et al., *Proc. Natl. Acad. Sci. USA* 81:7041-7045, 1983; Grant et al., *Nucl. Acids Res.* 15:5496, 1987) and a mouse  $V_H$  promoter (Loh et al., *Cell* 33:85-93, 1983). The choice of promoter will depend, at least in part, upon the level of expression desired or the recipient cell line to be transfected.

20 Such expression vectors may also contain a set of RNA splice sites located downstream from the promoter and upstream from the DNA sequence encoding the peptide or protein of interest. Preferred RNA splice sites may be obtained from adenovirus and/or immunoglobulin genes. Also contained in the expression vectors is a polyadenylation signal located downstream of the coding sequence of interest. Suitable polyadenylation signals include the early or late polyadenylation signals from SV40 (Kaufman and Sharp, *ibid.*), the polyadenylation signal from the Adenovirus 5 E1B region and the human growth hormone gene terminator (DeNoto et al., *Nuc. Acids Res.* 9:3719-3730, 1981). The expression vectors may include a noncoding viral leader sequence, such as the Adenovirus 2 tripartite leader, located between the promoter and 30 the RNA splice sites. Preferred vectors may also include enhancer sequences, such as

or  $V_L$  domain where these are capable of independently binding antigen with acceptable affinity. Alternatively the V region domain may be dimeric and contain  $V_H-V_H$ ,  $V_H-V_L$ , or  $V_L-V_L$  dimers in which the  $V_H$  and  $V_L$  chains are non-covalently associated (abbreviated hereinafter as  $F_v$ ). Where desired, however, the chains may be covalently coupled either directly, for example via a disulphide bond between the two variable domains, or through a linker, for example a peptide linker, to form a single chain domain (abbreviated hereinafter as  $scF_v$ ).

The variable region domain may be any naturally occurring variable domain or an engineered version thereof. By engineered version is meant a variable region domain which has been created using recombinant DNA engineering techniques. Such engineered versions include those created for example from natural antibody variable regions by insertions, deletions or changes in or to the amino acid sequences of the natural antibodies. Particular examples of this type include those engineered variable region domains containing at least one CDR and optionally one or more framework amino acids from one antibody and the remainder of the variable region domain from a second antibody.

The variable region domain may be covalently attached at a C-terminal amino acid to at least one other antibody domain or a fragment thereof. Thus, for example where a  $V_H$  domain is present in the variable region domain this may be linked to an immunoglobulin  $C_{H1}$  domain or a fragment thereof. Similarly a  $V_L$  domain may be linked to a  $C_K$  domain or a fragment thereof. In this way for example the antibody may be a Fab fragment wherein the antigen binding domain contains associated  $V_H$  and  $V_L$  domains covalently linked at their C-termini to a  $CH1$  and  $C_K$  domain respectively. The  $CH1$  domain may be extended with further amino acids, for example to provide a hinge region domain as found in a Fab' fragment, or to provide further domains, such as antibody  $CH2$  and  $CH3$  domains.

Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction



to synthesize the variable region from RNA of antibody-producing cells (see, for example, Larrick et al., *Methods: A Companion to Methods in Enzymology* 2:106, 1991; Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in *Monoclonal Antibodies: Production, Engineering and Clinical Application*, Ritter et al. (eds.), page 155-166 (Cambridge University Press 1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in *Monoclonal Antibodies: Principles and Applications*, Birch et al. (eds.), page 137 (Wiley-Liss, Inc. 1995)).

Antibodies for use in the invention may in general be monoclonal (prepared by conventional immunisation and cell fusion procedures) or in the case of fragments, derived therefrom using any suitable standard chemical e.g., reduction or enzymatic cleavage and/or digestion techniques, for example by treatment with pepsin.

More specifically, monoclonal anti-MMP-25 antibodies can be generated utilizing a variety of techniques. Rodent monoclonal antibodies to specific antigens may be obtained by methods known to those skilled in the art (see, for example, Kohler et al., *Nature* 256:495, 1975; and Coligan et al. (eds.), *Current Protocols in Immunology*, 1:2.5.1-2.6.7 (John Wiley & Sons 1991) ["Coligan"]; Picksley et al., "Production of monoclonal antibodies against proteins expressed in *E. coli*," in *DNA Cloning 2: Expression Systems*, 2nd Edition, Glover et al. (eds.), page 93 (Oxford University Press 1995)).

The affinity of a monoclonal antibody or binding partner, as well as inhibition of binding can be readily determined by one of ordinary skill in the art (see Scatchard, *Ann. N.Y. Acad. Sci.* 51:660-672, 1949).

Monoclonal antibodies may also be readily generated using techniques described for example, U.S. Patent NOS. 4,902,614, 4,543,439, and 4,411,993 which are incorporated herein by reference; see also *Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses*, Plenum Press, Kennett, McKearn, and Bechtol (eds.), 1980; and *Antibodies: A Laboratory Manual*, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, 1988, which are also incorporated herein by reference).

mouse and human variable regions including, among others, primers for  $V_{Ha}$ ,  $V_{Hb}$ ,  $V_{Hc}$ ,  $V_{Hd}$ ,  $C_{H1}$ ,  $V_L$  and  $C_L$  regions. These primers may be utilized to amplify heavy or light chain variable regions, which may then be inserted into vectors such as ImmunoZAP™ H or ImmunoZAP™ L (Stratagene), respectively. These vectors may then be introduced into *E. coli*, yeast, or mammalian-based systems for expression. Utilizing these techniques, large amounts of a single-chain protein containing a fusion of the  $V_H$  and  $V_L$  domains may be produced (see Bird et al., *Science* 242:423-426, 1988). In addition, such techniques may be utilized to change a "murine" antibody to a "human" antibody, without altering the binding specificity of the antibody.

Once suitable antibodies have been obtained, they may be isolated or purified by many techniques well known to those of ordinary skill in the art (see *Antibodies: A Laboratory Manual*, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, 1988). Suitable techniques include peptide or protein affinity columns, HPLC or RP-HPLC, purification on protein A or protein G columns, or any combination of these techniques.

In addition, an anti-MMP-25 antibody of the present invention may be derived from a human monoclonal antibody. Human monoclonal antibodies are obtained from transgenic mice that have been engineered to produce specific human antibodies in response to antigenic challenge. In this technique, elements of the human heavy and light chain locus are introduced into strains of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy chain and light chain loci. The transgenic mice can synthesize human antibodies specific for human antigens, and the mice can be used to produce human antibody-secreting hybridomas. Methods for obtaining human antibodies from transgenic mice are described, for example, by Green et al., *Nature Genet.* 7:13, 1994; Lonberg et al., *Nature* 368:856, 1994; and Taylor et al., *Int. Immun.* 6:579, 1994.

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography (see, for example, Coligan at pages 2.7.1-2.7.12 and

pages 2.9.1-2.9.3; Baines et al., "Purification of Immunoglobulin G (IgG)," in *Methods in Molecular Biology*, Vol. 10, pages 79-104 (The Humana Press, Inc. 1992)).

For particular uses, it may be desirable to prepare fragments of anti-MMP-25 antibodies. Such antibody fragments can be obtained, for example, by proteolytic hydrolysis of the antibody. Antibody fragments can be obtained by pepsin or papain digestion of whole antibodies by conventional methods. As an illustration, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S fragment denoted  $F(ab')_2$ . This fragment can be further cleaved using a thiol reducing agent to produce 3.5S  $Fab'$  monovalent fragments. Optionally, the cleavage reaction can be performed using a blocking group for the sulfhydryl groups that result from cleavage of disulfide linkages. As an alternative, an enzymatic cleavage using pepsin produces two monovalent Fab fragments and an Fc fragment directly. These methods are described, for example, by Goldenberg, U.S. Patent No. 4,331,647, Nisonoff et al., *Arch. Biochem. Biophys.* 89:230, 1960, Porter, *Biochem. J.* 73:119, 1959, Edelman et al., in *Methods in Enzymology* 1:422 (Academic Press 1967), and by Coligan at pages 2.8.1-2.8.10 and 2.10.-2.10.4.

Other methods of cleaving antibodies, such as separation of heavy chains to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody.

Alternatively, the antibody may be a recombinant or engineered antibody obtained by the use of recombinant DNA techniques involving the manipulation and re-expression of DNA encoding antibody variable and/or constant regions. Such DNA is known and/or is readily available from DNA libraries including for example phage-antibody libraries (see Chiswell, D.J. and McCafferty, J. *Tibtech.* 10:80-84 (1992)) or where desired can be synthesised. Standard molecular biology and/or chemistry procedures may be used to sequence and manipulate the DNA, for example, to introduce codons to create cysteine residues, to modify, add or delete other amino acids or domains as desired.

In this practice, one or more replicable expression vectors containing the DNA may be prepared and used to transform an appropriate cell line, e.g., a non-producing myeloma cell line, such as a mouse NSO line or a bacterial, e.g., *E. coli* line, in which production of the antibody will occur. In order to obtain efficient transcription and translation, the DNA sequence in each vector should include appropriate regulatory sequences, particularly a promoter and leader sequence operably linked to the variable domain sequence. Particular methods for producing antibodies in this way are generally well known and routinely used. For example, basic molecular biology procedures are described by Maniatis *et al* (Molecular Cloning, Cold Spring Harbor Laboratory, New York, 1989); DNA sequencing can be performed as described in Sanger *et al.* (*PNAS* 74:5463 (1977)) and the Amersham International plc sequencing handbook; and site directed mutagenesis can be carried out according to the method of Kramer *et al.* (*Nucl. Acids Res.* 12:9441 (1984)) and the Anglian Biotechnology Ltd handbook. Additionally, there are numerous publications, detailing techniques suitable for the preparation of antibodies by manipulation of DNA, creation of expression vectors and transformation of appropriate cells, for example as reviewed by Mountain A and Adair, J R in *Biotechnology and Genetic Engineering Reviews* (ed. Tombs, M P, 10, Chapter 1, 1992; Intercept, Andover, UK) and in International Patent Specification No. WO 91/09967.

Where desired, the antibody according to the invention may have one or more effector or reporter molecules attached to it and the invention extends to such modified proteins. The effector or reporter molecules may be attached to the antibody through any available amino acid side-chain, terminal amino acid or, where present carbohydrate functional group located in the antibody, always provided of course that this does not adversely affect the binding properties and eventual usefulness of the molecule. Particular functional groups include, for example any free amino, imino, thiol, hydroxyl, carboxyl or aldehyde group. Attachment of the antibody and the effector and/or reporter molecule(s) may be achieved via such groups and an appropriate functional group in the effector or reporter molecules. The linkage may be direct or indirect, through spacing or bridging groups.

Effector molecules include, for example, antineoplastic agents, toxins (such as enzymatically active toxins of bacterial or plant origin and fragments thereof e.g., ricin and fragments thereof) biologically active proteins, for example enzymes, nucleic acids and fragments thereof, e.g., DNA, RNA and fragments thereof, naturally occurring and synthetic polymers e.g., polysaccharides and polyalkylene polymers such as poly(ethylene glycol) and derivatives thereof, radionuclides, particularly radioiodide, and chelated metals. Suitable reporter groups include chelated metals, fluorescent compounds or compounds which may be detected by NMR or ESR spectroscopy.

Particular antineoplastic agents include cytotoxic and cytostatic agents, for example alkylating agents, such as nitrogen mustards (e.g., chlorambucil, melphalan, mechlorethamine, cyclophosphamide, or uracil mustard) and derivatives thereof, triethylenephosphoramide, triethylenethiophosphoramide, busulphan, or cisplatin; antimetabolites, such as methotrexate, fluorouracil, floxuridine, cytarabine, mercaptopurine, thioguanine, fluoroacetic acid or fluorocitric acid, antibiotics, such as bleomycins (e.g., bleomycin sulphate), doxorubicin, daunorubicin, mitomycins (e.g., mitomycin C), actinomycins (e.g., dactinomycin), plicamycin, calichaemicin and derivatives thereof, or esperamicin and derivatives thereof; mitotic inhibitors, such as etoposide, vincristine or vinblastine and derivatives thereof; alkaloids, such as ellipticine; polyols such as taxicin-I or taxicin-II; hormones, such as androgens (e.g., dromostanolone or testolactone), progestins (e.g., megestrol acetate or medroxyprogesterone acetate), estrogens (e.g., dimethylstilbestrol diphosphate, polyestradiol phosphate or estramustine phosphate) or antiestrogens (e.g., tamoxifen); anthraquinones, such as mitoxantrone, ureas, such as hydroxyurea; hydrazines, such as procarbazine; or imidazoles, such as dacarbazine.

Particularly useful effector groups are calichaemicin and derivatives thereof (see for example South African Patent Specifications NOS. 85/8794, 88/8127 and 90/2839).

Chelated metals include chelates of di-or tripositive metals having a coordination number from 2 to 8 inclusive. Particular examples of such metals include technetium (Tc), rhenium (Re), cobalt (Co), copper (Cu), gold (Au), silver (Ag), lead (Pb),

bismuth (Bi), indium (In), gallium (Ga), yttrium (Y), terbium (Tb), gadolinium (Gd), and scandium (Sc). In general the metal is preferably a radionuclide. Particular radionuclides include  $^{99m}\text{Tc}$ ,  $^{186}\text{Re}$ ,  $^{188}\text{Re}$ ,  $^{58}\text{Co}$ ,  $^{60}\text{Co}$ ,  $^{67}\text{Cu}$ ,  $^{195}\text{Au}$ ,  $^{199}\text{Au}$ ,  $^{110}\text{Ag}$ ,  $^{203}\text{Pb}$ ,  $^{206}\text{Bi}$ ,  $^{207}\text{Bi}$ ,  $^{111}\text{In}$ ,  $^{67}\text{Ga}$ ,  $^{68}\text{Ga}$ ,  $^{88}\text{Y}$ ,  $^{90}\text{Y}$ ,  $^{160}\text{Tb}$ ,  $^{153}\text{Gd}$  and  $^{47}\text{Sc}$ .

5 The chelated metal may be for example one of the above types of metal chelated with any suitable polydentate chelating agent, for example acyclic or cyclic polyamines, polyethers (e.g., crown ethers and derivatives thereof); polyamides; porphyrins; and carbocyclic derivatives.

In general, the type of chelating agent will depend on the metal in use. One particularly useful group of chelating agents in conjugates according to the invention, however, are acyclic and cyclic polyamines, especially polyaminocarboxylic acids, for example diethylenetriaminepentaacetic acid and derivatives thereof, and macrocyclic amines, e.g., cyclic tri-aza and tetra-aza derivatives (for example as described in International Patent Specification No. WO 92/22583); and polyamides, especially desferrioxamine and derivatives thereof.

Thus for example, when it is desired to use a thiol group in the antibody as the point of attachment this may be achieved through reaction with a thiol reactive group present in the effector or reporter molecule. Examples of such groups include an  $\alpha$ -halocarboxylic acid or ester, e.g., iodoacetamide, an imide, e.g., maleimide, a vinyl sulphone, or a disulphide. These and other suitable linking procedures are generally and more particularly described in International Patent Specifications NOS. WO 93/06231, WO 92/22583, WO 90/091195 and WO 89/01476.

#### RIBOZYMES AND ANTISENSE MOLECULES

25 In another aspect, the nucleic acid sequences of the present invention provide for nucleic acids useful for modulating or inhibiting the expression of a MMP-25 polypeptide in a cell. More specifically, the invention provides for a ribozyme that cleaves RNA encoding the aforementioned MMP-25 polypeptides. Also included is a nucleic acid molecule comprising a sequence that encodes such a ribozyme and a vector comprising the nucleic acid molecule. In a similar aspect, the invention provides

antisense nucleic acid molecule comprising a sequence that is antisense to a portion of the MMP-25 nucleic acids described herein. Also included are a vector comprising the antisense molecule, and vectors wherein the aforementioned ribozyme or antisense nucleic acid is operably linked to a promoter. Typical embodiments of these vectors are selected from the group consisting of plasmid vectors, phage vectors, herpes simplex viral vectors, adenoviral vectors, adenovirus-associated viral vectors and retroviral vectors. Host cells comprising the above vectors are also included.

Antisense oligonucleotide molecules are provided which specifically inhibit expression of MMP-25 nucleic acid sequences (*see generally*, Hirashima et al. in *Molecular Biology of RNA: New Perspectives* (M. Inouye and B. S. Dudoock, eds., 1987 Academic Press, San Diego, p. 401); *Oligonucleotides: Antisense Inhibitors of Gene Expression* (J.S. Cohen, ed., 1989 MacMillan Press, London); Stein and Cheng, *Science* 261:1004-1012, 1993; WO 95/10607; U.S. Patent No. 5,359,051; WO 92/06693; and EP-A2-612844). Briefly, such molecules are constructed such that they are complementary to, and able to form Watson-Crick base pairs with, a region of transcribed MMP-25 mRNA sequence. The resultant double-stranded nucleic acid interferes with subsequent processing of the mRNA, thereby preventing protein synthesis (Example 6).

Ribozymes are provided which are capable of inhibiting expression of MMP-25 RNA. As used herein, "ribozymes" are intended to include RNA molecules that contain anti-sense sequences for specific recognition, and an RNA-cleaving enzymatic activity. The catalytic strand cleaves a specific site in a target RNA at greater than stoichiometric concentration. A wide variety of ribozymes may be utilized within the context of the present invention, including for example, the hammerhead ribozyme (for example, as described by Forster and Symons, *Cell* 48:211-220, 1987; Haseloff and Gerlach, *Nature* 328:596-600, 1988; Walbot and Bruening, *Nature* 334:196, 1988; Haseloff and Gerlach, *Nature* 334:585, 1988); the hairpin ribozyme (for example, as described by Haseloff et al., U.S. Patent No. 5,254,678, issued October 19, 1993 and Hempel et al., European Patent Publication No. 0 360 257, published March 26, 1990); and *Tetrahymena* ribosomal RNA-based ribozymes (see Cech et al.,

hydroxyamino)-2R-isobutyl-3S-(thiopen-2-ylthiomethyl)-succinyl-L-phenylalanine-N-methylamidecarboxyalkylamino-based compounds such as N-1-(R)-carboxy-3-(1,3-dihydro-2H-benzfisoindol-2-yl)propyl-N',N'-dimethyl-L-leucinamide, trifluoroacetate (*J. Med. Chem.* 36:4030-4039, 1993); marimastat (BB-2516); N-chlorotaurine; eicosapentaenoic acid; matlystatin-B; actinonin (3-1-2-(hydroxymethyl)-1-pyrrolidinylcarbonyl-octanohydroxamic acid); N-phosphonalkyl dipeptides such as N-N-((R)-1-phosphonopropyl)-(S)-leucyl-(S)-phenylalanine-N-methylamide (*J. Med. Chem.* 37:158-169, 1994); peptidyl hydroxamic acids such as pNH.sub.2 -Bz-Gly-Pro-D-Leu-D-Ala-NHOH (*Biophys. Biochem. Res. Comm.* 199:1442-1446, 1994); Ro-31-7467, also known as 2-(5-bromo-2,3-dihydro-6-hydroxy-1,3-dioxo-1H-benzdelisoquinolin-2-yl)methyl(hydroxy)-phosphinyl-N-(2-oxo-3-azacyclotridecanyl)-4-methylvaleramide; CT1166, also known as N1N2-(morpholinosulphonylamino)-ethyl-3-cyclohexyl-2-(S)-propanamidyl-N4-hydroxy-2-(R)-3-(4-methylphenyl)propylsuccinamide (*Biochem. J.* 308:167-175, 1995); bromocyclic-adenosine monophosphate; protocatechuic aldehyde (3,4-dihydroxybenzaldehyde); estramustine (estradiol-3-bis(2-chloroethyl)carbamate); tetracycline (4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide); minocycline (7-dimethylamino-6-dimethyl-6-deoxytetracycline); methacycline (6-methylene oxytetracycline); and doxycycline (alpha-6-deoxy-5-hydroxytetracycline). Preferably, the inhibitor of an MMP includes an inhibitor other than an unsaturated fatty acid such as eicosapentaenoic acid.

Other inhibitors include tetracycline derivatives described in U.S. Patent No. 5,837,696 to Golub et al., which are disclosed to be useful for inhibiting MMP activity in cancer cells. Other classes of MMP inhibitors include the aryl-sulfonyl and related compounds described in U.S. Patent No. 5,866,587 to de Nanteuil et al. Others include those described by Gowravaram, *J. Med. Chem.* 38:2570-2581 (1995), which describes the development of a series of hydroxamates that inhibit MMPs and mentions thiols, phosphonates, phosphinates, phosphoramidates and N-carboxy alkyls as known MMP inhibitors. This reference indicates that MMP inhibitors typically may include a moiety that chelates zinc and a peptidic fragment that binds a subset of the specificity



pockets of MMPs. Hodgson, *Biotechnology* 13:554-557 1995 (1995), reviews the clinical status of several MMP inhibitors, including Galardin, Batimastat, and Marimastat. Further MMP inhibitors include butanediamide (Conway et al., *J. Exp. Med.* 182:449-457 (1995)), TIMPs (Mauch et al., *Arch. Dermatol. Res.* 287:107-114 (1994)), and retinoids (Fanjul et al., *Nature* 372:107-111 (1994); Nicholson et al., *EMBO Journal* 9(13):4443-4454 (1990); and Bailly, C. et al., *J. Investig. Derm.* 94(1):47-51 (1990)).

Indirect inhibitors may also be used, which include for example, inhibitors of transcription factors such as AP-1 NF-kappa B, and the cascade of factors regulated thereby which are involved in MMP regulation as mentioned in U.S. Patent No. 5,837,224. Hill, P. A. et al., *Biochem. J.* 308:167-175 (1995), describes two MMP inhibitors, CT1166 and RO317467, that may regulate MMP transcription factors.

The inhibitor may inhibit multiple types of MMPs, for example, MMP-1 (interstitial collagenase), MMP-2 (72 kD collagenase), MMP-3 (stromelysin), MMP-4 (telopeptidase), MMP-5 (collagen endopeptidase), MMP-6 (acid metalloproteinase), MMP-7 (uterine metalloproteinase), MMP-8 (neutrophil collagenase), and/or MMP-9 (92 kD collagenase). Inhibitors are preferably selected which preferentially inhibit MMP-25 over the non-type 25 MMPs.

In another embodiment of the method, the inhibitor agent is a nucleic acid or product encoded thereby which is delivered and expressed in the cell by a vector. More specifically, this embodiment of inhibiting the expression of a metalloproteinase includes the steps of administering to the cell a vector comprising a nucleic acid means for inhibiting expression of a MMP-25 polypeptide. Embodiments of this method include those where the nucleic acid means comprises a ribozyme that cleaves an RNA encoding the MMP-25 polypeptide or comprises a molecule that is antisense to a portion of an RNA encoding the MMP-25 polypeptide. In other embodiments of this method, the nucleic acid means is a non-functional variant of a MMP-25 polypeptide. Particularly useful non-functional variants include variants of the amino acid sequence according to SEQ ID NO:2, SEQ ID NO:4 or SEQ ID NO:6;  
(b) an amino acid sequence having at least 50% identity to the polypeptide of (a) or (b);

EXAMPLES

## EXAMPLE 1

## CLONING OF A LONG MMP-25 cDNA - MMP-25(I)

A first matrix metalloproteinase, herein designated as MMP-25(I), was identified. The polynucleotide encodes a protein comprising the conserved peptide sequences LVAAHELGHXLGLXHSXXXXAXMSSSY (SEQ ID NO:7) and HGDXXPFDGXXXXLAHAFXP GXGGDXHPDXDEXWT (SEQ ID NO:8) where X is any amino acid. These conserved peptide sequences represent a consensus for MMP polypeptides as determined by aligning protein sequences of several MMP family members using a multiple sequence alignment program. The consensus sequence is representative of conserved amino acid residues within two separate Zn-binding domains, both of which are ordinarily present on MMPs.

The first MMP sequence identified comprised 833 bp (SEQ ID NO:1). To obtain a full-length cDNA sequence for the novel MMP, a mammary gland cDNA expression library was screened by amplification using RACE reactions with unique sequence primers deduced from the 833 bp sequence in combination with primers that bind to 5' and 3' vector sequences adjacent to the ends of cloned inserts. In particular, the vector primer AP1 (Clontech, Palo Alto, CA) was used with one of the following primers from the candidate 833 bp sequence to amplify the 5' sequences:

GSP1: 8563 TGATATCATAATAGATCCTCCATAGGTGCC SEQ ID NO:9  
 GSP 2: 8564 TTCCTTAGGCAGACCTCCATAGATGGACTGG SEQ ID NO:10

Similarly, the vector primer AP2 (Clontech, Palo Alto, CA) was used with one of the following primers from the candidate 833 bp sequence to amplify the 3' sequences:

GSP3: 7433 CCTAAGGAACCTGCTAAGCCAAAGGAA SEQ ID NO:11  
 GSP4: 7560 CCGCAGAGAAGTAATGTTCTTTAAA SEQ ID NO:12

Typical RACE reaction conditions were used to amplify cloned sequences, e.g., 35 cycles of a 30 second denaturation followed by a 4 minute extension at between 68 and 72°C. Amplified nucleic acids were isolated and sequenced.

5 Using the above method, a novel sequence of 1833 bp in length (SEQ ID NO:5) with an open reading frame of 1539 bp (position 12 to 1550 of SEQ ID NO:5) was identified (see, Figure 2). SEQ ID NO:5 also contained a poly-A tail with a polyadenylation sequence (ATTAAA) located 24 bp upstream (see, Figure 2), indicative of a true cDNA.

## 10 IDENTIFICATION OF MMP-25 (s)

A second novel metalloproteinase sequence, herein designated MMP-25(s), was also identified by cDNA library screening using RACE reactions as described in EXAMPLE 1. The nucleotide sequence encoding MMP-25(s) is shown in SEQ ID NO:3 and the encoded amino sequence encoded is shown in SEQ ID NO:4. The nucleotide sequence of MMP-25(s) was identical to the sequence for MMP-25(l) except in having a deletion of 129 nucleotides corresponding to 43 amino acids. The deleted sequence in the shorter version of MMP-25 is unique among metalloproteinases: while the encoded protein contains the first Zn-binding domain, it lacks the second Zn/Ca-binding domain typical for other members of the matrix metalloproteinase family as illustrated in Figure 3.

## 20 EXAMPLE 3

### TISSUE EXPRESSION PATTERNS OF MMP-25 SEQUENCES

The MMP nucleic acids and polypeptides of the present invention have a unique pattern of tissue expression in human tissue as illustrated in Figure 4. RT-PCR reactions using reverse transcriptase were performed on RNA samples isolated from a tissue panel from 36 normal tissues. Figure 4 illustrates that both the long and short

variants of MMP-25 were expressed in fetal skin and mammary glands after 35 cycles of amplification, but were poorly detected in other tissues.

The expression in skin tissue is localized in skin follicle cells as illustrated by in situ hybridization results illustrated in Figure 4. Briefly, fetal skin samples fixed in 4% paraformaldehyde, embedded in paraffin and cut into 5  $\mu$ m sections were obtained from Biochain Inc. (San Leandro, CA) Sections were deparaffinized with xylene and rehydrated using standard procedures. Single-stranded digoxigenin-containing (Roche Molecular Biochemicals (Indianapolis, IN) sense and antisense riboprobes were made in vitro using linear templates of MMP-25 DNA and T7 RNA polymerase. Reaction yield and integrity were assessed by gel electrophoresis.

Tissue sections were washed in 10 mM Tris (pH 7.5), 150 mM NaCl for 5 min, followed by a 2 hr blocking step using normal sheep serum (3% final) Sigma, St. Louis MO) and 0.035 Triton in 10 mM Tris (pH 7.5) 150 mM NaCl. The slides were incubated with alkaline phosphatase-conjugated anti-DIG antibody (Roche Molecular Biochemicals) at a 1/200 dilution overnight at 4°C in 10 mM Tris (pH 7.5), 150 mM NaCl supplemented with 1% normal sheep serum. Reference sequential-sections were stained with hemotoxylin and mounted for visualization by light microscopy.

The in situ hybridization results revealed that MMP-25 was expressed in the inner root sheath layer of the hair follicle as shown in Figure 5. The cell layer within the inner root sheath, the Henle layer, was further defined as a particular cell type for MMP-25 mRNA expression in skin. The particular localization of MMP-25 expression in inner root sheath of hair follicles indicates that control of the expression of the MMP-25 sub-family of metalloproteinases is involved in the regulation of hair growth.

#### EXAMPLE 4

##### CHROMOSOMAL LOCATION FOR HUMAN MMP-25

A chromosomal location of MMP-25 was determined using two primers unique to MMP-25 nucleic acids. The primers DMO 7560 (SEQ ID NO:13) and DMO 8563 (SEQ ID NO:14) were used to screen a G3 radiation hybrid panel to map the

location of MMP-25. MMP-25 maps to chromosome 11q22, a region where several other MMPs including MMP1, MMP3, MMP7, MMP8, MMP10, MMP12, and MMP13, have been previously mapped.

5

## EXAMPLE 5

## METHOD OF MODULATING HAIR GROWTH

In one practice of an improved method of modulating hair growth, a dermatologically acceptable composition comprising a known MMP inhibitor is applied in an amount that inhibits the activity of MMP-25 to a greater extent than it inhibits the activity of other MMPs. Such an inhibitor is preferably incorporated into a topical composition adapted for application to the skin.

The amount of inhibitor that preferentially inhibits MMP-25 is determined by assessing the level of reduced MMP catalytic activity against a panel of known MMP enzymes. The zymography procedure described in U.S. Patent No. 5,962,466 is used to assess relative catalytic activity of the 54 KD MMP-25(1) of the present invention in comparison to the activity of the 72kD MMP-2 and 92 kD MMP-9 present in extracts of skin tissue.

Briefly, hair follicles are removed from mammalian skin and homogenized in a non-denaturing buffer, for example a buffer containing 25 mM Tris, H 7.5 and 50 mM sucrose. The samples are prepared for SDS gel electrophoresis and separated on an SDS polyacrylamide gel containing a suitable amount of MMP substrate (e.g., 0.1% gelatin) incorporated therein. The separated proteins are renatured within the gel by incubation with a suitable renaturing buffer such as 2.5% Triton X-100, and renatured in the presence of a buffer containing test amounts of selected MMP inhibitors, for example 0.01 - 10 mM tetracycline, minocyclene, doxycycline, methacycline or 1,10-phenanthroline. The gel is developed in suitable buffer for detecting MMP activity, such as 10 mM Tris base, 40 mM Tris HCl, 200 mM NaCl, 5 mM  $\text{CaCl}_2$  and 0.02% Brij 35.

The relative levels of MMP activity and level of inhibition are assessed by detecting the presence and size of "ghost bands" corresponding to the positions of

antisense oligonucleotide results in a 25% change in either instance compared to the control scrambled oligonucleotide.

In providing the foregoing description of the invention, citation has been made to several references that will aid in the understanding or practice thereof. All such references are incorporated by reference herein.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

## CLAIMS

1. An isolated nucleic acid molecule consisting essentially of a nucleotide sequence selected from the group consisting of:

- (a) a nucleotide sequence according to SEQ ID NOs:1, 3 and 5
- (b) a nucleotide sequence having at least 85% identity to the nucleotide sequence according to SEQ ID NOs:1, 3 and 5;
- (c) complements of a sequences according to SEQ ID NO:1, 3 and 5; and
- (d) sequences that hybridizes to a sequence according to SEQ ID NO:1, 3 and 5 under conditions of normal stringency.

2. A polypeptide comprising an amino acid sequence selected from the group consisting of:

- (a) an amino acid sequence according to SEQ ID NOs:2, 4 and 6;
- (b) an amino acid sequence having at least 90% identity to the amino acid sequence according to SEQ ID NOs:2, 4 and 6;
- (c) a nucleotide sequence encoded by a nucleic acid molecule according to claim 1; and
- (d) a nucleotide sequence having at least 85% identity to the nucleotide sequence encoded by a nucleic acid molecule according to claim 1; and
- (e) an amino acid sequence encoded by a nucleic acid that hybridizes under conditions of normal stringency to the nucleic acid molecule according to claim 1.

3. A method of identifying a nucleic acid molecule encoding all or a part of a metalloproteinase, comprising:

- (1) hybridizing a nucleic acid molecule sample to the nucleic acid molecule according to claim 1 and;

(b) a polypeptide comprising a first matrix metalloproteinase Zn-binding domain with the proviso that the polypeptide lacks a second matrix metalloproteinase Zn-binding domain; and

(c) an amino acid sequence encoded by a nucleic acid that hybridizes under conditions of high stringency to a nucleic acid molecule according to claim 1.

19. The method of claim 17, wherein said nucleic acid molecule encodes a ribozyme that cleaves a RNA encoding the matrix metalloproteinase -25 polypeptide.

20. The method of claim 17, wherein said nucleic acid molecule contains a sequence that is antisense to a portion of a RNA encoding the matrix metalloproteinase -25 polypeptide.

21. A method of modulating hair growth in a mammal, comprising applying a dermatologically acceptable composition comprising an inhibitor of a matrix metalloproteinase, with the proviso that the applied composition reduces the catalytic activity of a type 25 matrix metalloproteinase to a greater extent than it reduces the catalytic activity of at least one non-type 25 matrix metalloproteinase.

22. A polypeptide according to claim 2, wherein said polypeptide has a first matrix metalloproteinase Zn-binding domain and lacks a second matrix metalloproteinase Zn-binding domain.

23. The polypeptide of claim 22, wherein said polypeptide exhibits a catalytic activity of a matrix metalloproteinase.

24. The polypeptide of claim 22, wherein said polypeptide lacks a catalytic activity of a matrix metalloproteinase.



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## Initial assembled sequence

[Strand]

```
1  AGAAAATACC CACTTCTCA GGATGATATC AATGGAATCC AGTCCATCTA TGGAGGTCTG
61  CCTAAGGAAC CTGCTAAGCC AAAGGAACCC ACTATACCCC ATGCCTGTGA CCCTGACTTG
121 ACTTTTGACG CTATCACAAC TTTCCGAGCA GAAGTAATGT TCTTTAAAGG CAGGCACCTA
181 TGGAGGATCT ATTATGATAT CACGGATGTT GAGTTTGAAT TAATTGCTTC ATTCTGGCCA
241 TCTCTGCCAG CTGATCTGCA AGCTGCATAC GAGAACCCCA GAGATAAGAT TCTGGTTTTT
301 AAAGATGAAA ACTTCTGGAT GATCAGAGGA TATGCTGTCT TGCCAGATTA TCCCAAATCC
361 ATCCATACAT TAGGTTTTCC AGGACGTGTG AAGAAAATAG ATGCAGCCGT CTGTGATAAG
421 ACCACAAGAA AAACCTACTT CTTTGTGGGC ATTTGGTGCT GGAGGTTTGA TGAATGACC
481 CAAACCATGG ACAAGGGTT CCCGCAGAGA GTGGTAAAC ACTTTCCTGG AATCAGTATC
541 CGTGTTGATG CTGCTTTCCA GTACAAGGA TTCTTCTTTT TCAGCCGTGG ATCAACGCAA
601 TTTGAATACG ACATTAAGAC AAAGAATATT ACCCGAATCA TGAGAACTAA TACTTGTTTT
661 CAATGCAAAG AACCAAAGAA CTCCTCATTT GGTTTTGATA TCAACAAGGA AAAAGCACAT
721 TCAGGAGGCA TAAAGATATT GTATCATAAG AGTTTAAGCT TGTATTATTT TGGTATTGTT
781 CATTTGCTGA AAAACACTTC TATTATCAA TAAATTCATA GACCTAAAT AAA
```

*Fig. 1*

gaaagagagg a atg aag cgc ctt ctg ctt ctg ttt ttg ttc ttt ata aca	50
<u>Met Lys Arg Leu Leu Leu Leu Phe Leu Phe Ile Thr</u>	
1 5 10	
ttt tct tct gca ttt ccc tta gtc cgg atg atg gaa aat gaa gaa aat	98
<u>Phe Ser Ser</u> Ala Phe Pro Leu Val Arg Met Met Glu Asn Glu Glu Asn	
15 20 25	
gtg caa ctg gct cag gca tat ctc aac cag ttc tac tct ctt gaa ata	146
Val Gln Leu Ala Gln Ala Tyr Leu Asn Gln Phe Tyr Ser Leu Glu Ile	
30 35 40 45	
gaa ggg aat cat ctt gtt caa agc aag aat agg agt ctc ata gat gac	194
Glu Gly Asn His Leu Val Gln Ser Lys Asn Arg Ser Leu Ile Asp Asp	
50 55 60	
aaa att cgg gaa atg caa gca ttt ttt gga ttg aca gtg act gga aga	242
Lys Ile Arg Glu Met Gln Ala Phe Phe Gly Leu Thr Val Thr Gly Arg	
65 70 75	
ctg gac tca aac acc ctt gag atc atg aag aca ccc agg tgt ggg gtg	290
Leu Asp Ser Asn Thr Leu Glu Ile Met Lys Thr <u>Pro Arg Cys Gly Val</u>	
80 85 90	
cct gat gtg ggc cag tat ggc tac acc ctc cct ggg tgg aga aaa tac	338
<u>Pro Asp</u> Val Gly Gln Tyr Gly Tyr Thr Leu Pro Gly Trp Arg Lys Tyr	
95 100 105	
aac ctc acc tac aga ata ata aac tat act ccg gat atg gca cga gct	386
Asn Leu Thr Tyr Arg Ile Ile Asn Tyr Thr Pro Asp Met Ala Arg Ala	
110 115 120 125	
gct gtg gat gag gct atc caa gaa ggt tta gaa gtg tgg agc aaa gtc	434
Ala Val Asp Glu Ala Ile Gln Glu Gly Leu Glu Val Trp Ser Lys Val	
130 135 140	
act cca cta aaa ttc acc aag att tca aag ggg att gca gac atc atg	482
Thr Pro Leu Lys Phe Thr Lys Ile Ser Lys Gly Ile Ala Asp Ile Met	
145 150 155	

*Fig. 2A*

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att gcc ttt agg act cga gtc cat ggt cgg tgt cct cgc tat ttt gat 530  
 Ile Ala Phe Arg Thr Arg Val His Gly Arg Cys Pro Arg Tyr Phe Asp  
 160 165 170

ggt ccc ttg gga gtt ctt ggc cat gcc ttt cct cct ggt ccg ggt ctg 578  
 Gly Pro Leu Gly Val Leu Gly His Ala Phe Pro Pro Gly Pro Gly Leu  
 175 180 185

ggt ggt gac act cat ttt gat gag gat gaa aac tgg acc aag gat gga 626  
 Gly Gly Asp Thr His Phe Asp Glu Asp Glu Asn Trp Thr Lys Asp Gly  
 190 195 200 205

gca gga ttc aac ttg ttt ctt gtg gct gct cat gaa ttt ggt cat gca 674  
 Ala Gly Phe Asn Leu Phe Leu Val Ala Ala His Glu Phe Gly His Ala  
 210 215 220

ctg ggg ctc tct cac tcc aat gat caa aca gcc ttg atg ttc cca aat 722  
 Leu Gly Leu Ser His Ser Asn Asp Gln Thr Ala Leu Met Phe Pro Asn  
 225 230 235

tat gtc tcc ctg gat ccc aga aaa tac cca ctt tct cag gat gat atc 770  
 Tyr Val Ser Leu Asp Pro Arg Lys Tyr Pro Leu Ser Gln Asp Asp Ile  
 240 245 250

aat gga atc cag tcc atc tat gga ggt ctg cct aag gaa cct gct aag 818  
 Asn Gly Ile Gln Ser Ile Tyr Gly Gly Leu Pro Lys Glu Pro Ala Lys  
 255 260 265

cca aag gaa ccc act ata ccc cat gcc tgt gac cct gac ttg act ttt 866  
 Pro Lys Glu Pro Thr Ile Pro His Ala Cys Asp Pro Asp Leu Thr Phe  
 270 275 280 285

gac gct atc aca act ttc cgc aga gaa gta atg ttc ttt aaa ggc agg 914  
 Asp Ala Ile Thr Thr Phe Arg Arg Glu Val Met Phe Phe Lys Gly Arg  
 290 295 300

cac cta tgg agg atc tat tat gat atc acg gat gtt gag ttt gaa tta 962  
 His Leu Trp Arg Ile Tyr Tyr Asp Ile Thr Asp Val Glu Phe Glu Leu  
 305 310 315

*Fig. 2B*

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att gct tca ttc tgg cca tct ctg cca gct gat ctg caa gct gca tac 1010  
 Ile Ala Ser Phe Trp Pro Ser Leu Pro Ala Asp Leu Gln Ala Ala Tyr  
 320 325 330

gag aac ccc aga gat aag att ctg gtt ttt aaa gat gaa aac ttc tgg 1058  
 Glu Asn Pro Arg Asp Lys Ile Leu Val Phe Lys Asp Glu Asn Phe Trp  
 335 340 345

atg atc aga gga tat gct gtc ttg cca gat tat ccc aaa tcc atc cat 1106  
 Met Ile Arg Gly Tyr Ala Val Leu Pro Asp Tyr Pro Lys Ser Ile His  
 350 355 360 365

aca tta ggt ttt cca gga cgt gtg aag aaa ata gat gca gcc gtc tgt 1154  
 Thr Leu Gly Phe Pro Gly Arg Val Lys Lys Ile Asp Ala Ala Val Cys  
 370 375 380

gat aag acc aca aga aaa acc tac ttc ttt gtg ggc att tgg tgc tgg 1202  
 Asp Lys Thr Thr Arg Lys Thr Tyr Phe Val Gly Ile Trp Cys Trp  
 385 390 395

agg ttt gat gaa atg acc caa acc atg gac aaa ggg ttc ccg cag aga 1250  
 Arg Phe Asp Glu Met Thr Gln Thr Met Asp Lys Gly Phe Pro Gln Arg  
 400 405 410

gtg gta aaa cac ttt cct gga atc agt atc cgt gtt gat gct gct ttc 1298  
 Val Val Lys His Phe Pro Gly Ile Ser Ile Arg Val Asp Ala Ala Phe  
 415 420 425

cag tac aaa gga ttc ttc ttt ttc agc cgt gga tca acg caa ttt gaa 1346  
 Gln Tyr Lys Gly Phe Phe Phe Phe Ser Arg Gly Ser Thr Gln Phe Glu  
 430 435 440 445

tac gac att aag aca aag aat att acc cga atc atg aga act aat act 1394  
 Tyr Asp Ile Lys Thr Lys Asn Ile Thr Arg Ile Met Arg Thr Asn Thr  
 450 455 460

tgg ttt caa tgc aaa gaa cca aag aac tcc tca ttt ggt ttt gat atc 1442  
 Trp Phe Gln Cys Lys Glu Pro Lys Asn Ser Ser Phe Gly Phe Asp Ile  
 465 470 475

*Fig. 2C*

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aac aag gaa aaa gca cat tca gga ggc ata aag ata ttg tat cat aag 1490  
 Asn Lys Glu Lys Ala His Ser Gly Gly Ile Lys Ile Leu Tyr His Lys  
 480 485 490

agt tta agc ttg ttt att ttt ggt att gtt cat ttg ctg aaa aac act 1538  
 Ser Leu Ser Leu Phe Ile Phe Gly Ile Val His Leu Leu Lys Asn Thr  
 495 500 505

tct att tat caa taaattcata gacctaaaat aaacctcaac aggtctttta 1590  
 Ser Ile Tyr Gln  
 510

atataaattc tgcttcaaaa tagaataaaa ccattcttta acaacaagtt gctggtccta 1650  
 gttctaaata tccaaattca atggccattt tgagctgcct gattctttta ataggaagtt 1710  
 attatgtaga aacaaaaatc tctgactgta cttaagcct atttcatgct ttgtggactt 1770  
 ggagaagaca tgtcttataa ctgaataactg aaacatttat taaaccaatc tttagcattc 1830  
 tg 1832

*Fig. 2D*

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176	V.QEVPYEDIRLRQKE	VL.ASGF.DS	SP	TG.F.A.YF	A.P.FSSTD	MTM2HUM.PRO		
164	T.EEVPYSELENGK-RDV	P.I.ASGF.DS	SP	EG.F.A.YF	S.P.LGNPNH	MTM3HUM.PRO		
88	N.HE	VA	GST	Q.D.SKAD.NDG	YP	G.TVA.F.HHTA	D.A.FRSSD	MMP 17P
141	T.QEV	QA.A	RLS.HG.QSSY	SNT	GR.A.DI.EL	SV	F.EGT	MMP 18P
150	N.RL	HD	S.GIKE.DF	YP	S.L.A	N.Y.A	D.T.SSSK	MMP 20P
78	G.T.HE	VDSPPQGEP	L.D.ARAF.QDS	YP	LG.T.A	F.EHPIS	DE.T.FGSKA	MMP 21P
126	FS.REVA	PEQPS	LR.G.YPIN.TD.LVSALHHC	T.E.A	F.PH	GI	DS.Y.VLGPTR	MMP 22P
156	R.SR	HD.E	N.GRWE.DG	YP	KD.L.A	A.T.V	S.D.L.LGEGQVVRVRYGNADG	GELAHUM.PRO
153	T.RV	YSRD	V.Q.GVAE.DG	YP	KD.L.A	IQ.A	D.L.SLGKGVVPTFRFGNADG	GELBHUM.PRO
206								contig 355 long
263								contig 355 short
208								COLL1HUM.PRO
207								COLL2HUM.PRO
212								COLL3HUM.PRO
208								MATRUM.PRO
208								METAHUM.PRO
208								STO1HUM.PRO
207								STO2HUM.PRO
203								STO3HUM.PRO
228								MTM1HUM.PRO
248								MTM2HUM.PRO
235								MTM3HUM.PRO
152								MMP 17P
201								MMP 18P
212								MMP 20P
145								MMP 21P

Fig. 3C

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194	-----YSW-----	MMP 22P
231	EYCKFPFLNGKEYNSCTDTGRSDGLWGSTTYNFEKDGKYGFCPHEALFTMGNAEQPCKFPRFQGTYSDCSTTEGRTDGYRWGTT	GELAHUM. PRO
228	AACHFPFIFEGRSYACTTDGRSDGLPWCS TTANVYD TDRFGFCPSERLYTRDGNADGKPCQFPFIFQGSYSACTTDGRSDGYRWCAAT	GELB HUM. PRO
207	-----GFNLEFLVAHEFGHAL-----	contig 355 long
164	-----	contig 355 short
209	-----EY. HR. . . L. S.-----	COLL1HUM. PRO
208	-----NY. . . S.-----	COLL2HUM. PRO
213	-----Y. . . S.-----	COLL3HUM. PRO
212	-----T. L. S.-----	MATRHUM. PRO
209	-----T. T. V. I. S.-----	METAHUM. PRO
209	-----T. . . I. S.-----	STO1HUM. PRO
208	-----T. . . L. S.-----	STO2HUM. PRO
204	-----DQ. TD. LQ. . . V.-----	STO3HUM. PRO
229	-----N. NDI. . . V. L.-----	MTM1HUM. PRO
249	-----H. N. . . V. L.-----	MTM2HUM. PRO
236	-----D. ND. . . V. L.-----	MTM3HUM. PRO
153	-----AH. MD. A. V. . . I.-----	MMP 17P
203	-----V. RII. . . V.-----	MMP 18P
213	-----Y. . . S.-----	MMP 20P
146	-----SQQLE-----Q. LAGG-----	MMP 21P
197	-----KKGWJ-----	MMP 22P
321	EDYDRDKKYGFCPETAMSTV - GGNSEGAPCVFPFTFLGNKYESCTSAGRSDGKMYMCATTANYDDDRKMGFCPDQ. YS. M	GELAHUM. PRO
318	ANVDRDKLFGFCPTRADSTVNGGNSAGELCVFPFTFLGKEYSTCTSEGRDGRLLWCATTSMFDSDDKKMGFCPDQ. YS. M	GELB HUM. PRO

Fig. 3D

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223	GLSHNDQ TALMFNPVVS-L-DPRKYPLS-QDDINGIQSIYGG-----LPKEPAKPEKPTIP-----	contig 355 long
180		contig 355 short
225	...T.IG...Y.S.-T-F--SGDVQ.A--D...A...RSQNPVQ-----IG.QT-----	COLL1HUM.PRO
224	...A.S.PG...Y...-A-FRETSN.S.P--D...D...A...LSSNPIQ-----TG.ST-----	COLL2HUM.PRO
229	...D.K.PG...I...-T-YTGKSHFM.P--D.VQ...L...PGDE-----DPN.H.KT-----	COLL3HUM.PRO
221	MG.S.PN.V.Y.T.-G-NG.QNFK.--K...KL-----	MATRUM.PRO
225	...G.S.PK.V...T.K--YV.INTER.--A...R...L...DPKENQRLP-----NPDNSE-----	METAHUM.PRO
225	...F.ANTE...Y.L.H.-T.LTRFR-----L...PPDSPETP.VPTEPV.P.GT-----	STO1HUM.PRO
224	...F.ANTE...Y.L.N.-FTELAQFR.--V...L...PPASTEER.VPTKSV.SGSEM-----	STO2HUM.PRO
222	...O.TTAAK.SAF-----TFR...LSP.CR.V.HL.QP--WPTVTSRT-----	STO3HUM.PRO
246	...E.S.PS.I.A.F.Q--WM.TENFV.P--D.RR...QL...ESG-----FPTKM.PQ.-RT-SRPSVPDKPKNPT-----	MTM1HUM.PRO
266	...E.SNP.N.I.A.F.Q--WK.VDNFK.P--E.LR...QL...TPDGQPOPTQ.LPTVT.RR.GR.-DHRPPRPPOPPPGGKPERPKP-----	MTM2HUM.PRO
254	...E...P...I.A.F.Q--YME-QTLQ.P--N.YR--HOR.MSPDKIPPTR.LPTV.-PHRS.-PADPRKNDRKPPRPPTGRPSYP-----	MTM3HUM.PRO
171	...VAAHSI.R.Y.QGPVG..LR.G.PYE.-KVR-VWQL.VRESVSPTAQ.E-----	MMP 17P
219	...G.RYSQ...A.V.EG---YRPHFK.H--P.VA...AL...KKSPIRDEEEE.TEL.TV.PV.TEPS-----	MMP 18P
229	...D.K.PG...I...-T-YTGKSHFM.P--D.VQ...L...PGDE-----DPN.H.KT-----	MMP 20P
157	...PVDEELGFS-----	MMP 21P
218	...M.QHGR...-----H.NATLRGKALS.ELW.LHRL..C-----LDRLFVCASWARRGF-----	MMP 22P
410	...E.Q.PG...A.I.-T-YT--KNFR.--K...EL...ASP-----ID.GTG.TPTLG.VT-----	GELAHUM.PRO
408	...D.SVPE...Y.M.R--FTEGP--H--K.V...RHL...PRPEPRPPTTTTPQ.TA.PTVCPTGPPTVHPSPERTAGPTGPPSA-----	GELBHM.PRO
277	-----HACD--PDLTFDAITTFRRVNFVKGRHLWR-IYYDITDVE-FELIASFWPSLP---ADLQAAAYENP-----	contig 355 long
234	-----	contig 355 short
276	...K...SK...I.G...D.FYM.-TNPFEY.-LNF.SV.Q...--NG.E...FAD-----	COLL1HUM.PRO
277	...KP...S...L.G.IL...D.YF.-RHPQLQR.-MNF.SL...--TGI...DFD-----	COLL2HUM.PRO
282	...DK...S.SL...SL.G.T.I...D.FF.-LHPQQV.A.-LF.TK...E...--NRID...H.S-----	COLL3HUM.PRO
259	-----	MATRUM.PRO

Fig. 3E



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280 -----AL.---N.S..V.VGNKIF..D.FF.L-KVSRPKTS-VN..S.L..T.---SGIE...IEA METAHUM.PRO  
 288 -----AN.---A.S..VS.L.G.II.D.F..KSLRKLEP..LH..S.---SGVD...VTS STO1HUM.PRO  
 287 -----AK.---A.S..S.L.G.YL..D.YF..RSHWNEP..H..SA.---SY.D...VNS STO2HUM.PRO  
 269 -PALGPQAGIDTNEIAPLEDPAPDA--CEAS..VS.I.G.L.F..AGFV..L.RGGQLQPGYPA.ASRH.OG.---SPVD..F.DAQ STO3HUM.PRO  
 314 -----YGP-----NI.---GN.---TVAML.G.MFV..E.WF..VRNNQVM.GYMPM-GQ..RG.---SINT..RKD MTM1HUM.PRO  
 351 GPPVQPRATERPDQYGP-----NI.---G.---TVAML.G.MFV..WF..VRHNRVL.NYMPM-GH..RG.---G.IS...RQD MTM2HUM.PRO  
 334 GAK-----P-----NI.---GN.---NTLAIL..MFV.DQWF..VRNRRVM.GYPMQ-TY..RG.---PSID.V..SD MTM3HUM.PRO  
 225 -PPLLPEPPDNRSSAPP--RKDVPHR--CSTH..VAQI.G.A.F..KYF..LTRDRHLVSLQPAQMRH..RG..LHLDSD.V..RTS MMP 17P  
 285 -----MPDP.S--SE.D-AMMLGP.GKTYA..DYV.TVSDS---GPGPLFRVSAL.EG..GNLD--A.V.S--R MMP 18P  
 282 -----DK.---S.SL...SL.G.T.I..D.FF..LHPQQV.A.-LF.TK..E.---NRID..H.S MMP 20P  
 167 -----G-----G-----RWV.L-----MMP 21P  
 271 -----CDARRRLMKRLCP--SS..FCYEFP.PTVA.TPPP-----TKTRLVPEGRNVTFRCG MMP 22P  
 467 -----EI.K-Q.IV.G.AQI.G.IF..D.FI..TVTPRDKPMG-PL.V.T..E.---EKID.V..A.Q GELAHUM.PRO  
 492 GPTGPTAGPSTATTVPLSPVDD..N--VNI--AEIGNQLYL..DGKY..FSEGRGSRPQGP..DK..A.---RK.DSVF.E.L GELBHM.PRO

342 RDKTLVFKDENFWMIRGYAVLDPYPKSIHT-LGFGPRVKKIDAACVCK-TTRKTYFFVGIGCWRFDEMTQTMKGGFPQRVVKHFGISIR contig 355 long  
 294 -----EVRF..GNKY.AVQ.QN..HG..D.YSSF..RT..H..LSEE-N.G..ANKY..Y.YKRS..P.Y.KMIAHD...GHK contig 355 short  
 337 -----L.FL..GNQY.ALS..DI.OG..D.-SNY..SS.QA..F---YRS..NDQF..Y.NQR.F.EP.Y.KSISGA...ESK COLLIHUM.PRO  
 338 -----H.L.FI.RGRK..ALN..DI.EG..K.-SE..L.KE..S..HFE-D.G..LL.S.NQV..Y.DTNHI...DY.RLIEED...GDK COL2HUM.PRO  
 261 -----NQVFL..DKY.L.SNLRPE.N...S-F..NF...FNP-RFYR...DNOY..Y..RR.M..P.Y.KLIT.N.Q..GPK COL3HUM.PRO  
 341 K.LVFI..GNO..A..NE.RAG..RG...PT.R...IS..EKN...EDKY...KRNS.EP..KOIAED...DSK MATRUM.PRO  
 349 -----TVFI..GNE..A..NE.QAG..RG...PTIR...S..EKK...AADKY...NS.S.EQ..RLIADD...VEPK METAHUM.PRO  
 352 GH-WF.QGAQY.VYD.EKPVLG..APL-E..LVRFP--VH..LVNGPEKN..I..R.RDY...HPS.RRV.SPV.R.ATD-WR.VPSE STO1HUM.PRO  
 377 GKVF-..GDH.VFEASLE.G..H.-KE..RGLPTD...LFWM-PNG...R.NKYY..N.ELRAV.SEY.KNIKV-WE..PES STO2HUM.PRO  
 428 GRVF-..GDY.LF.EANLE.G..QPL-SY.LGTPYDR..T.IWME-P.GH.F..QEDRY..N.E..RG.P.Y.KPISV-WQ..PAS STO3HUM.PRO  
 398 GNVF-..GNKY.VFKDITLQ.G..HDL-IT..SGIPPHG..S.IWME-DVG...K.DRY..YS.EMK...P.Y.KPITV-WK..PES MTM1HUM.PRO  
 398 GNVF-..GNKY.VFKDITLQ.G..HDL-IT..SGIPPHG..S.IWME-DVG...K.DRY..YS.EMK...P.Y.KPITV-WK..PES MTM2HUM.PRO  
 398 GNVF-..GNKY.VFKDITLQ.G..HDL-IT..SGIPPHG..S.IWME-DVG...K.DRY..YS.EMK...P.Y.KPITV-WK..PES MTM3HUM.PRO

Fig. 3F

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310	DH..VF..GDRV.VFKDWN.EEG..RPV-SDFS.L.PGG--	.....FSWA-HNDR.....KDQLY..Y.DH.RH..P.Y.AQSPL-WR.VPST	MMP 17P
356	TQW.HF..GDKV.RYINFKMS.GF..KLN-----RSEPNL.....LYM-PLNQ.VFL.K.SGY.QW..LAR.DFSSY.KPIKGL.T.VPNQ		MMP 18P
343	H.L.FI.RGRK..ALN..DI.EG..K.-SE..L.KE....S...HFE-D.G..LL.S.NQV..Y.DTNHI...DY.RLIEED....GDK		MMP 20P
174	-----		MMP 21P
323	-Q...HK.GKVY.....KQEPLEFSY.....	.....YALGEA.LSI.ANA	MMP 22P
529	EE.AVF.AGNEY.IYSASTLERG..PL-.S..L.PD.QRV...FNWS-KNK...I.A.DKF..YN.VKK..P...KLIADAMNA.PDN		GELAHUM.PRO
576	SK.LFF.SGRQV.VYT.AS..G--.RRLD-K..LGAD.AQVTG.LR-S.GRG.MLL.S.RRL....VKA.MV.PRSASE.DRM...VPLD		GELBHM.PRO
425	VDAAFQYK--GFF-----FFSRGSTQFEYDIKTKNITRIMRTNT-----WFQCKEP-----KN		contig 355 long
382	-----		contig 355 short
426	...V.--MKD.....Y.FH.TR.YKF.P...R.LTLOKA.S-----N.RKN		COLLIHUM.PRO
424	...V.--QOEH.....HVFS.PRYAYF.LIAQRV..VA.G.K-----LN.RYG		COLL2HUM.PRO
431	...VY--EKN.YI-----Y.FN.PI.....S.WSNR.V.V.PA.S-----ILW.		COLL3HUM.PRO
267	-----		MATRUM.PRO
429	I..V.-.SKNKYY-----Y.FQ..N.....FLLQR..KTLKS.S-----G.		METAHUM.PRO
437	I..V.--EEF.....Y.FT..S.L.F.PNA.KV.HTLKS.S-----LN.		STO1HUM.PRO
436	...VL--QAF.....Y.FS..S...F.PNARWV.H.LKS.S-----LH.		STO2HUM.PRO
436	I.....DADGY-----AY.L..RLYWKF.PVKVKALE-GFPRLVGPDF.G.A..ANTLL		STO3HUM.PRO
463	PRGS.MGDEV.....TY.YK.NKYWKFNQKL-KVEPGYPKSALRD.MG.....PSGGRP-----DEGTEETEVIIEVDEEG		MTM1HUM.PRO
514	PKG..LSNDAAY-----TY.YK.TKYWKF.NERL-RMEPGYPKSILRDFMG.Q.HVEPGRPWDVARPPFNPHGGAEPGADSAEGDVGDD		MTM2HUM.PRO
484	PQG..VH.EN.....TY.YKEGVL-.IQTRYSRLEPGHPRSIKDLG.D---GPTDRVKEGHSPP-----DDVD---		MTM3HUM.PRO
395	L.D.MRWSDGA-----SY.F..QEYWKVLDGELEVAP-GYPQSTARD.LV.GDSQADGS-----VAAGVDAEGRAPPGQHDQSR		MMP 17P
429	PS..MSWQDG-----RVY.FK.KVYWRLN-QQLRVEKGYPRNISHN.MH.RPRTIDTTPSGGNTTPS-----		MMP 18P
431	...VY--EKN.YI-----Y.FN.PI.....S.WSNR.V.V.PA.S-----ILW.		MMP 20P
175	-----		MMP 21P
363	N-----EGTYTC-----		MMP 22P
617	L..WDLQGG.HS-----Y.FK.AYLLKENQSLKSVKFGSIKS--D.LG.		GELAHUM.PRO

Fig. 3G

13/15

661 THDV...REKAY.CODR.YM.V.SRS.LN----QVQGVVY---DIL..P.D  
 471 SSFGFDINKEKAHSGGK-----ILYHKSLSLFI---FGIVHLLKNTS---IYQ  
 428 .....  
 426 .....  
 424 .....  
 431 .....  
 267 .....  
 429 .....  
 437 .....  
 436 .....  
 436 .....  
 536 GG-----AVSAAVLPVL.L.LVLAVGLAVFFRRHGTPRRL.C.RSLDKV  
 599 GD..AGV..DGGSRVVQVEEVARTVNVW.VPLL.L.CVLGLTYAL.QMQRKGAPRVL.CKRSLOEW  
 548 -----IV..LDNTASTVKAIA.VIPCI.A.CLLVLVTVFQFKRKGTPRHIL.CKRSMQEW  
 470 ED.YEVCSCS-----GASSPPGAPGP.VAATML.LLPPL-----PGALWTAQAALT--L  
 488 -----GT..TLDTTLSATETT-----FEY  
 175 .....  
 363 .....  
 617 .....  
 661 .....

GELBHUM.PRO  
 contig 355 long  
 contig 355 short  
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 COLL2HUM.PRO  
 COLL3HUM.PRO  
 MATRHUM.PRO  
 METAHUM.PRO  
 STO1HUM.PRO  
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Fig. 3H

## SEQUENCE LISTING

&lt;110&gt; Darwin Discovery Ltd.

Wang, Kai

Smith, Ryan

Fajardo, Mark

Moss, Patrick

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tat gga ggt ctg cct aag gaa cct gct aag cca aag gaa ccc act ata      96
Tyr Gly Gly Leu Pro Lys Glu Pro Ala Lys Pro Lys Glu Pro Thr Ile
      20              25              30

ccc cat gcc tgt gac cct gac ttg act ttt gac gct atc aca act ttc      144
Pro His Ala Cys Asp Pro Asp Leu Thr Phe Asp Ala Ile Thr Thr Phe
      35              40              45

cgc aga gaa gta atg ttc ttt aaa ggc agg cac cta tgg agg atc tat      192
Arg Arg Glu Val Met Phe Phe Lys Gly Arg His Leu Trp Arg Ile Tyr
      50              55              60

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Tyr Asp Ile Thr Asp Val Glu Phe Glu Leu Ile Ala Ser Phe Trp Pro
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Ser Leu Pro Ala Asp Leu Gln Ala Ala Tyr Glu Asn Pro Arg Asp Lys
      85              90              95

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Thr Tyr Phe Phe Val Gly Ile Trp Cys Trp Arg Phe Asp Glu Met Thr			
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Gly Ile Ser Ile Arg Val Asp Ala Ala Phe Gln Tyr Lys Gly Phe Phe			
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His Ala Cys Asp Pro Asp Leu Thr Phe Asp Ala Ile Thr Thr Phe Arg			
35	40	45	
Arg Glu Val Met Phe Phe Lys Gly Arg His Leu Trp Arg Ile Tyr Tyr			
50	55	60	

Asp Ile Thr Asp Val Glu Phe Glu Leu Ile Ala Ser Phe Trp Pro Ser  
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 85 90 95  
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 100 105 110  
 Leu Pro Asp Tyr Pro Lys Ser Ile His Thr Leu Gly Phe Pro Gly Arg  
 115 120 125  
 Val Lys Lys Ile Asp Ala Ala Val Cys Asp Lys Thr Thr Arg Lys Thr  
 130 135 140  
 Tyr Phe Phe Val Gly Ile Trp Cys Trp Arg Phe Asp Glu Met Thr Gln  
 145 150 155 160  
 Thr Met Asp Lys Gly Phe Pro Gln Arg Val Val Lys His Phe Pro Gly  
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 195 200 205  
 Ile Thr Arg Ile Met Arg Thr Asn Thr Trp Phe Gln Cys Lys Glu Pro  
 210 215 220  
 Lys Asn Ser Ser Phe Gly Phe Asp Ile Asn Lys Glu Lys Ala His Ser  
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&lt;400&gt; 3

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 agaaccaaaag aactcctcat ttgttttga tatcaacaag gaaaaagcac attcaggagg 1380  
 cataaagata ttgtatcata agagttaaag cttgtttatt ttgtgtattg ttcatttgct 1440  
 gaaaaacact tctattttatc aataaattca tagacctaaa ataaaaaa 1488

&lt;210&gt; 4

&lt;211&gt; 466

&lt;212&gt; PRT

&lt;213&gt; Homo sapien

&lt;400&gt; 4

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Met Lys Arg Leu Leu Leu Leu Phe Leu Phe Phe Ile Thr Phe Ser Ser
 1          5          10          15
Ala Phe Pro Leu Val Arg Met Met Glu Asn Glu Glu Asn Val Gln Leu
 20          25          30
Ala Gln Ala Tyr Leu Asn Gln Phe Tyr Ser Leu Glu Ile Glu Gly Asn
 35          40          45
His Leu Val Gln Ser Lys Asn Arg Ser Leu Ile Asp Asp Lys Ile Arg
 50          55          60
Glu Met Gln Ala Phe Phe Gly Leu Thr Val Thr Gly Arg Leu Asp Ser
 65          70          75          80
Asn Thr Leu Glu Ile Met Lys Thr Pro Arg Cys Gly Val Pro Asp Val
 85          90          95
Gly Gln Tyr Gly Tyr Thr Leu Pro Gly Trp Arg Lys Tyr Asn Leu Thr
100          105          110
Tyr Arg Ile Ile Asn Tyr Thr Pro Asp Met Ala Arg Ala Val Asp
115          120          125
Glu Ala Ile Gln Glu Gly Leu Glu Val Trp Ser Lys Val Thr Pro Leu
130          135          140
Lys Phe Thr Lys Ile Ser Lys Gly Ile Ala Asp Ile Met Ile Ala Phe
145          150          155          160
Arg Thr Arg Gly Phe Asn Leu Phe Leu Val Ala Ala His Glu Phe Gly
165          170          175
His Ala Leu Gly Leu Ser His Ser Asn Asp Gln Thr Ala Leu Met Phe
180          185          190
Pro Asn Tyr Val Ser Leu Asp Pro Arg Lys Tyr Pro Leu Ser Gln Asp
195          200          205
Asp Ile Asn Gly Ile Gln Ser Ile Tyr Gly Gly Leu Pro Lys Glu Pro
210          215          220
Lys Pro Lys Glu Pro Thr Ile Pro His Ala Cys Asp Pro Asp Leu Thr
225          230          235          240
Phe Asp Ala Ile Thr Thr Phe Arg Arg Glu Val Met Phe Phe Lys Gly
245          250          255
Arg His Leu Trp Arg Ile Tyr Tyr Asp Ile Thr Asp Val Glu Phe Glu
260          265          270
Leu Ile Ala Ser Phe Trp Pro Ser Leu Pro Asp Leu Gln Ala Ala Tyr
275          280          285
Glu Asn Pro Arg Asp Lys Ile Leu Val Phe Lys Asp Glu Asn Phe Trp
290          295          300
Met Ile Arg Gly Tyr Ala Val Leu Pro Asp Tyr Pro Lys Ser Ile His
305          310          315          320
Thr Leu Gly Phe Pro Gly Arg Val Lys Lys Ile Asp Ala Ala Val Cys
325          330          335
Asp Lys Thr Thr Arg Lys Thr Tyr Phe Phe Val Gly Ile Trp Cys Trp
340          345          350
Arg Phe Asp Glu Met Thr Gln Thr Met Asp Lys Gly Phe Pro Gln Arg
355          360          365
Val Val Lys His Phe Pro Gly Ile Ser Ile Arg Val Asp Ala Ala Phe
370          375          380
Gln Tyr Lys Gly Phe Phe Phe Phe Arg Gly Ser Thr Gln Phe Glu Tyr
385          390          395          400
Asp Ile Lys Thr Lys Asn Ile Thr Arg Ile Met Arg Thr Asn Thr Trp

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405 410 415  
 Phe Gln Cys Lys Glu Pro Lys Asn Ser Ser Phe Gly Phe Asp Ile Asn  
 420 425 430  
 Lys Glu Lys Ala His Ser Gly Gly Ile Lys Ile Leu Tyr His Lys Ser  
 435 440 445  
 Ser Leu Phe Ile Phe Gly Ile Val His Leu Leu Lys Asn Thr Ser Ile  
 450 455 460  
 Tyr Gln  
 465

<210> 5  
 <211> 1841  
 <212> DNA  
 <213> Homo sapien

<400> 5  
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 tcaaccagtt ctactctctt gaaatagaag ggaatcatct tgttcaaagc aagaatagga 180  
 gtctcataga tgacaaaatt cgggaaatgc aagcattttt tggattgaca gtgactggaa 240  
 gactggactc aaacaccctt gagatcatga agacaccagc gtgtgggggtg cctgatgtgg 300  
 gccagtatgg ctacaccctc cctgggtgga gaaaatacaa cctcacctac agaataataa 360  
 actatactcc ggatatggca cgagctgctg tggatgagggc tatccaagaa ggtttagaag 420  
 tgtggagcaa agtcaactca ctaaaattca ccaagatttc aaaggggatt gcagacatca 480  
 tgattgcctt taggactcga gtccatggtc ggtgtcctcg ctattttgat ggtcccttgg 540  
 gagttccttg ccattgcctt cctcctggtc cgggtctggg tgggtgacact cattttgatg 600  
 aggatgaaaa ctggaccaag gatggagcag gattcaactt gtttcttgtg gctgctcatg 660  
 aatttggcca tgcaactggg ctctctcact ccaatgatca aacagccttg atgttcccaa 720  
 attatgtctc cctggatccc agaaaatacc cactttotca ggatgatatac aatggaatcc 780  
 agtccatcta tggaggctcg cctaaggaac ctgctaagcc aaaggaaccc actatacccc 840  
 atgcctgtga cctgacttg acttttgacg ctatcacaaac tttccgcaga gaagtaatgt 900  
 tctttaaagg caggcaccta tggaggatct attatgatata cacggatgtt gagtttgaat 960  
 taattgcttc attctggcca tctctgccag ctgatctgca agctgcatac gagaacccca 1020  
 gagataagat tctggttttt aaagatgaaa acttctggat gatcagagga tatgctgtct 1080  
 tgccagatta tcccaaattc atccatacat taggttttcc aggacgtgtg aagaaaatag 1140  
 atgcagccgt ctgtgataag accacaagaa aaacctaactt ctttgtgggc atttgggtgt 1200  
 ggaggtttga tgaatgacc caaacatgg acaaagggtt cccgcagaga gtggtaaaac 1260  
 actttcctgg aatcagatc cgtgttgatg ctgctttcca gtacaaagga ttcttctttt 1320  
 tcagccgtgg atcaacgcaa ttgaaatag acattaagac aaagaatatt acccgaatca 1380  
 tgagaactaa tacttggtt caatgcaaag aaccaagaa ctcctcattt ggttttgata 1440  
 tcaacaagga aaaagcacat tcaggaggca taaagatatt gtatcataag agtttaagct 1500  
 tgtttatttt tggattgtt catttgctga aaaacacttc tatttatcaa taaattcata 1560  
 gacctaaaat aaacctcaac aggtctttta atataaattc tgcttcaaaa tagaataaaa 1620  
 ccattcttta acaacaagtt gctggtccta gttctaaata tccaaattca atggccattt 1680  
 tgagctgcct gattctttta ataggaagtt attatgtaga aacaaaaatc tctgactgta 1740  
 ctttaagcct atttcatgct ttgtggactt ggagaagaca tgtcttataa ctgaatactg 1800  
 aaacatttat taaaccaatc tttagcattc tgaaaaaaa a 1841

<210> 6  
 <211> 513  
 <212> PRT  
 <213> Homo sapien

<400> 6  
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 Ala Phe Pro Leu Val Arg Met Met Glu Asn Glu Glu Asn Val Gln Leu  
 20 25 30



Ala Gln Ala Tyr Leu Asn Gln Phe Tyr Ser Leu Glu Ile Glu Gly Asn  
 35 40 45  
 His Leu Val Gln Ser Lys Asn Arg Ser Leu Ile Asp Asp Lys Ile Arg  
 50 55 60  
 Glu Met Gln Ala Phe Phe Gly Leu Thr Val Thr Gly Arg Leu Asp Ser  
 65 70 75 80  
 Asn Thr Leu Glu Ile Met Lys Thr Pro Arg Cys Gly Val Pro Asp Val  
 85 90 95  
 Gly Gln Tyr Gly Tyr Thr Leu Pro Gly Trp Arg Lys Tyr Asn Leu Thr  
 100 105 110  
 Tyr Arg Ile Ile Asn Tyr Thr Pro Asp Met Ala Arg Ala Ala Val Asp  
 115 120 125  
 Glu Ala Ile Gln Glu Gly Leu Glu Val Trp Ser Lys Val Thr Pro Leu  
 130 135 140  
 Lys Phe Thr Lys Ile Ser Lys Gly Ile Ala Asp Ile Met Ile Ala Phe  
 145 150 155 160  
 Arg Thr Arg Val His Gly Arg Cys Pro Arg Tyr Phe Asp Gly Pro Leu  
 165 170 175  
 Gly Val Leu Gly His Ala Phe Pro Pro Gly Pro Gly Leu Gly Gly Asp  
 180 185 190  
 Thr His Phe Asp Glu Asp Glu Asn Trp Thr Lys Asp Gly Ala Gly Phe  
 195 200 205  
 Asn Leu Phe Leu Val Ala Ala His Glu Phe Gly His Ala Leu Gly Leu  
 210 215 220  
 Ser His Ser Asn Asp Gln Thr Ala Leu Met Phe Pro Asn Tyr Val Ser  
 225 230 235 240  
 Leu Asp Pro Arg Lys Tyr Pro Leu Ser Gln Asp Asp Ile Asn Gly Ile  
 245 250 255  
 Gln Ser Ile Tyr Gly Gly Leu Pro Lys Glu Pro Ala Lys Pro Lys Glu  
 260 265 270  
 Pro Thr Ile Pro His Ala Cys Asp Pro Asp Leu Thr Phe Asp Ala Ile  
 275 280 285  
 Thr Thr Phe Arg Arg Glu Val Met Phe Phe Lys Gly Arg His Leu Trp  
 290 295 300  
 Arg Ile Tyr Tyr Asp Ile Thr Asp Val Glu Phe Glu Leu Ile Ala Ser  
 305 310 315 320  
 Phe Trp Pro Ser Leu Pro Ala Asp Leu Gln Ala Ala Tyr Glu Asn Pro  
 325 330 335  
 Arg Asp Lys Ile Leu Val Phe Lys Asp Glu Asn Phe Trp Met Ile Arg  
 340 345 350  
 Gly Tyr Ala Val Leu Pro Asp Tyr Pro Lys Ser Ile His Thr Leu Gly  
 355 360 365  
 Phe Pro Gly Arg Val Lys Lys Ile Asp Ala Ala Val Cys Asp Lys Thr  
 370 375 380  
 Thr Arg Lys Thr Tyr Phe Phe Val Gly Ile Trp Cys Trp Arg Phe Asp  
 385 390 395 400  
 Glu Met Thr Gln Thr Met Asp Lys Gly Phe Pro Gln Arg Val Val Lys  
 405 410 415  
 His Phe Pro Gly Ile Ser Ile Arg Val Asp Ala Ala Phe Gln Tyr Lys  
 420 425 430  
 Gly Phe Phe Phe Phe Ser Arg Gly Ser Thr Gln Phe Glu Tyr Asp Ile  
 435 440 445  
 Lys Thr Lys Asn Ile Thr Arg Ile Met Arg Thr Asn Thr Trp Phe Gln  
 450 455 460  
 Cys Lys Glu Pro Lys Asn Ser Ser Phe Gly Phe Asp Ile Asn Lys Glu  
 465 470 475 480  
 Lys Ala His Ser Gly Gly Ile Lys Ile Leu Tyr His Lys Ser Leu Ser  
 485 490 495

7

Leu Phe Ile Phe Gly Ile Val His Leu Leu Lys Asn Thr Ser Ile Tyr  
                   500                  505                  510  
 Gln

<210> 7  
 <211> 27  
 <212> PRT  
 <213> Homo sapien

<220>  
 <221> VARIANT  
 <222> (1)...(27)  
 <223> Xaa = any amino acid

<400> 7  
 Leu Val Ala Ala His Glu Leu Gly His Xaa Leu Gly Leu Xaa His Ser  
   1                  5                  10                  15  
 Xaa Xaa Xaa Xaa Ala Xaa Met Ser Ser Ser Tyr  
                   20                  25

<210> 8  
 <211> 37  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> VARIANT  
 <222> (1)...(37)  
 <223> Xaa = any amino acid

<400> 8  
 His Gly Asp Xaa Xaa Pro Phe Asp Gly Xaa Xaa Xaa Xaa Leu Ala His  
   1                  5                  10                  15  
 Ala Phe Xaa Pro Gly Xaa Gly Xaa Gly Gly Asp Xaa His Pro Asp Xaa  
                   20                  25                  30  
 Asp Glu Xaa Trp Thr  
                   35

<210> 9  
 <211> 30  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Primer

<400> 9  
 tgatatcata atagatcctc cataggtgcc

30

<210> 10  
 <211> 31  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> Primer

<400> 10  
 ttccttaggc agacctccat agatggactg g 31  
 <210> 11  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence  
 <220>  
 <223> Primer  
 <400> 11  
 cctaaggaac ctgctaagcc aaaggaa 27  
 <210> 12  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence  
 <220>  
 <223> Primer  
 <400> 12  
 ccgcagagaa gtaatgttct ttaaa 25  
 <210> 13  
 <211> 25  
 <212> DNA  
 <213> Artificial Sequence  
 <220>  
 <223> Primer  
 <400> 13  
 ccgcagagaa gtaatgttct ttaaa 25  
 <210> 14  
 <211> 30  
 <212> DNA  
 <213> Artificial Sequence  
 <220>  
 <223> Primer  
 <400> 14  
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 <210> 15  
 <211> 411  
 <212> DNA  
 <213> Homo sapien  
 <400> 15  
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 cctaaggaac ctgctaagcc aaaggaaccc actataccccc atgcctgtga cctgacttg 120  
 acttttgacg ctatcacaaac ttccgcaga gaagtaatgt tctttaaaagg caggcaccta 180  
 tggaggatct attatgatat cacggatgtt gagtttgaat taattgcttc attctggcca 240  
 tctctgccag ctgatctgca agctgcatac gagaacccca gagataagat tctgggtttt 300

aaagatgaaa acttctggat gatcagagga tatgctgtct tgccagatta tcccaaattcc 360  
atccatacat taggttttcc aggacgtgtg aagaaaatag atgcagccgt c 411

<210> 16

<211> 382

<212> DNA

<213> Homo sapiens

<400> 16

tttttttttt ttttttaggt ctatgaattt attgataaat agaagtgttt ttcagcaaat 60  
gaacaatacc aaaaataaac aagcttaaac tcttatgata caatatcttt atgcctcctg 120  
aatgtgcttt ttccttgttg atatcaaaac caaatgagga gttcttttgt tctttgcatt 180  
gaaaccaagt attagttctc atgattcggg taatattctt tgtcttaatg tcgtattcaa 240  
attgcgttga tccacggctg aaaaagaaga atcctttgta ctggaaagca gcatcaacac 300  
ggatactgat tccaggaaag tgttttacca ctctctgcgg gaaccctttg tccatggttt 360  
gggtcatttc atcaaaccctc ca 382

<210> 17

<211> 12

<212> PRT

<213> Homo sapien

<220>

<221> VARIANT

<222> (3)...(3)

<223> Xaa = any amino acid

<221> VARIANT

<222> (6)...(7)

<223> Xaa = any amino acid

<221> VARIANT

<222> (9)...(10)

<223> Xaa = any amino acid

<221> VARIANT

<222> (12)...(12)

<223> Xaa = Serine or Threonine

<400> 17

His Glu Xaa Phe His Xaa Xaa Gly Xaa Xaa His Xaa  
1 5 10

<210> 18

<211> 7

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (5)...(5)

<223> Xaa = any amino acid

<400> 18

Pro Arg Cys Gly Xaa Pro Asp  
1 5

<210> 19

&lt;211&gt; 469

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 19

Met His Ser Phe Pro Pro Leu Leu Leu Leu Phe Trp Gly Val Val  
 1 5 10 15  
 Ser His Ser Phe Pro Ala Thr Leu Glu Thr Gln Glu Gln Asp Val Asp  
 20 25 30  
 Leu Val Gln Lys Tyr Leu Glu Lys Tyr Tyr Asn Leu Lys Asn Asp Gly  
 35 40 45  
 Arg Gln Val Glu Lys Arg Arg Asn Ser Gly Pro Val Val Glu Lys Leu  
 50 55 60  
 Lys Gln Met Gln Glu Phe Phe Gly Leu Lys Val Thr Gly Lys Pro Asp  
 65 70 75 80  
 Ala Glu Thr Leu Lys Val Met Lys Gln Pro Arg Cys Gly Val Pro Asp  
 85 90 95  
 Val Ala Gln Phe Val Leu Thr Glu Gly Asn Pro Arg Trp Glu Gln Thr  
 100 105 110  
 His Leu Thr Tyr Arg Ile Glu Asn Tyr Thr Pro Asp Leu Pro Arg Ala  
 115 120 125  
 Asp Val Asp His Ala Ile Glu Lys Ala Phe Gln Leu Trp Ser Asn Val  
 130 135 140  
 Thr Pro Leu Thr Phe Thr Lys Val Ser Glu Gly Gln Ala Asp Ile Met  
 145 150 155 160  
 Ile Ser Phe Val Arg Gly Asp His Arg Asp Asn Ser Pro Phe Asp Gly  
 165 170 175  
 Pro Gly Gly Asn Leu Ala His Ala Phe Gln Pro Gly Pro Gly Ile Gly  
 180 185 190  
 Gly Asp Ala His Phe Asp Glu Asp Glu Arg Trp Thr Asn Asn Phe Arg  
 195 200 205  
 Glu Tyr Asn Leu His Arg Val Ala Ala His Glu Leu Gly His Ser Leu  
 210 215 220  
 Gly Leu Ser His Ser Thr Asp Ile Gly Ala Leu Met Tyr Pro Ser Tyr  
 225 230 235 240  
 Thr Phe Ser Gly Asp Val Gln Leu Ala Gln Asp Asp Ile Asp Gly Ile  
 245 250 255  
 Gln Ala Ile Tyr Gly Arg Ser Gln Asn Pro Val Gln Pro Ile Gly Pro  
 260 265 270  
 Gln Thr Pro Lys Ala Cys Asp Ser Lys Leu Thr Phe Asp Ala Ile Thr  
 275 280 285  
 Thr Ile Arg Gly Glu Val Met Phe Phe Lys Asp Arg Phe Tyr Met Arg  
 290 295 300  
 Thr Asn Pro Phe Tyr Pro Glu Val Glu Leu Asn Phe Ile Ser Val Phe  
 305 310 315 320  
 Trp Pro Gln Leu Pro Asn Gly Leu Glu Ala Ala Tyr Glu Phe Ala Asp  
 325 330 335  
 Arg Asp Glu Val Arg Phe Phe Lys Gly Asn Lys Tyr Trp Ala Val Gln  
 340 345 350  
 Gly Gln Asn Val Leu His Gly Tyr Pro Lys Asp Ile Tyr Ser Ser Phe  
 355 360 365  
 Gly Phe Pro Arg Thr Val Lys His Ile Asp Ala Ala Leu Ser Glu Glu  
 370 375 380  
 Asn Thr Gly Lys Thr Tyr Phe Phe Val Ala Asn Lys Tyr Trp Arg Tyr  
 385 390 395 400  
 Asp Glu Tyr Lys Arg Ser Met Asp Pro Gly Tyr Pro Lys Met Ile Ala  
 405 410 415  
 His Asp Phe Pro Gly Ile Gly His Lys Val Asp Ala Val Phe Met Lys

420 425 430  
 Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg Gln Tyr Lys Phe Asp  
 435 440 445  
 Pro Lys Thr Lys Arg Ile Leu Thr Leu Gln Lys Ala Asn Ser Trp Phe  
 450 455 460  
 Asn Cys Arg Lys Asn  
 465  
  
 <210> 20  
 <211> 467  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 20  
 Met Phe Ser Leu Lys Thr Leu Pro Phe Leu Leu Leu Leu His Val Gln  
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 Ile Ser Lys Ala Phe Pro Val Ser Ser Lys Glu Lys Asn Thr Lys Thr  
 20 25 30  
 Val Gln Asp Tyr Leu Glu Lys Phe Tyr Gln Leu Pro Ser Asn Gln Tyr  
 35 40 45  
 Gln Ser Thr Arg Lys Asn Gly Thr Asn Val Ile Val Glu Lys Leu Lys  
 50 55 60  
 Glu Met Gln Arg Phe Phe Gly Leu Asn Val Thr Gly Lys Pro Asn Glu  
 65 70 75 80  
 Glu Thr Leu Asp Met Met Lys Lys Pro Arg Cys Gly Val Pro Asp Ser  
 85 90 95  
 Gly Gly Phe Met Leu Thr Pro Gly Asn Pro Lys Trp Glu Arg Thr Asn  
 100 105 110  
 Leu Thr Tyr Arg Ile Arg Asn Tyr Thr Pro Gln Leu Ser Glu Ala Glu  
 115 120 125  
 Val Glu Arg Ala Ile Lys Asp Ala Phe Glu Leu Trp Ser Val Ala Ser  
 130 135 140  
 Pro Leu Ile Phe Thr Arg Ile Ser Gln Gly Glu Ala Asp Ile Asn Ile  
 145 150 155 160  
 Ala Phe Tyr Gln Arg Asp His Gly Asp Asn Ser Pro Phe Asp Gly Pro  
 165 170 175  
 Asn Gly Ile Leu Ala His Ala Phe Gln Pro Gly Gln Gly Ile Gly Gly  
 180 185 190  
 Asp Ala His Phe Asp Ala Glu Glu Thr Trp Thr Asn Thr Ser Ala Asn  
 195 200 205  
 Tyr Asn Leu Phe Leu Val Ala Ala His Glu Phe Gly His Ser Leu Gly  
 210 215 220  
 Leu Ala His Ser Ser Asp Pro Gly Ala Leu Met Tyr Pro Asn Tyr Ala  
 225 230 235 240  
 Phe Arg Glu Thr Ser Asn Tyr Ser Leu Pro Gln Asp Asp Ile Asp Gly  
 245 250 255  
 Ile Gln Ala Ile Tyr Gly Leu Ser Ser Asn Pro Ile Gln Pro Thr Gly  
 260 265 270  
 Pro Ser Thr Pro Lys Pro Cys Asp Pro Ser Leu Thr Phe Asp Ala Ile  
 275 280 285  
 Thr Thr Leu Arg Gly Glu Ile Leu Phe Phe Lys Asp Arg Tyr Phe Trp  
 290 295 300  
 Arg Arg His Pro Gln Leu Gln Arg Val Glu Met Asn Phe Ile Ser Leu  
 305 310 315 320  
 Phe Trp Pro Ser Leu Pro Thr Gly Ile Gln Ala Ala Tyr Glu Asp Phe  
 325 330 335  
 Asp Arg Asp Leu Ile Phe Leu Phe Lys Gly Asn Gln Tyr Trp Ala Leu  
 340 345 350

Ser Gly Tyr Asp Ile Leu Gln Gly Tyr Pro Lys Asp Ile Ser Asn Tyr  
 355 360 365  
 Gly Phe Pro Ser Ser Val Gln Ala Ile Asp Ala Ala Val Phe Tyr Arg  
 370 375 380  
 Ser Lys Thr Tyr Phe Phe Val Asn Asp Gln Phe Trp Arg Tyr Asp Asn  
 385 390 395 400  
 Gln Arg Gln Phe Met Glu Pro Gly Tyr Pro Lys Ser Ile Ser Gly Ala  
 405 410 415  
 Phe Pro Gly Ile Glu Ser Lys Val Asp Ala Val Phe Gln Gln Glu His  
 420 425 430  
 Phe Phe His Val Phe Ser Gly Pro Arg Tyr Tyr Ala Phe Asp Leu Ile  
 435 440 445  
 Ala Gln Arg Val Thr Arg Val Ala Arg Gly Asn Lys Trp Leu Asn Cys  
 450 455 460  
 Arg Tyr Gly  
 465

&lt;210&gt; 21

&lt;211&gt; 471

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 21

Met His Pro Gly Val Leu Ala Ala Phe Leu Phe Leu Ser Trp Thr His  
 1 5 10 15  
 Cys Arg Ala Leu Pro Leu Pro Ser Gly Asp Glu Asp Asp Leu Ser  
 20 25 30  
 Glu Glu Asp Leu Gln Phe Ala Glu Arg Tyr Leu Arg Ser Tyr Tyr His  
 35 40 45  
 Pro Thr Asn Leu Ala Gly Ile Leu Lys Glu Asn Ala Ala Ser Ser Met  
 50 55 60  
 Thr Glu Arg Leu Arg Glu Met Gln Ser Phe Phe Gly Leu Glu Val Thr  
 65 70 75 80  
 Gly Lys Leu Asp Asp Asn Thr Leu Asp Val Met Lys Lys Pro Arg Cys  
 85 90 95  
 Gly Val Pro Asp Val Gly Glu Tyr Asn Val Phe Pro Arg Thr Leu Lys  
 100 105 110  
 Trp Ser Lys Met Asn Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp  
 115 120 125  
 Met Thr His Ser Glu Val Glu Lys Ala Phe Lys Lys Ala Phe Lys Val  
 130 135 140  
 Trp Ser Asp Val Thr Pro Leu Asn Phe Thr Arg Leu His Asp Gly Ile  
 145 150 155 160  
 Ala Asp Ile Met Ile Ser Phe Gly Ile Lys Glu His Gly Asp Phe Tyr  
 165 170 175  
 Pro Phe Asp Gly Pro Ser Gly Leu Leu Ala His Ala Phe Pro Pro Gly  
 180 185 190  
 Pro Asn Tyr Gly Gly Asp Ala His Phe Asp Asp Asp Glu Thr Trp Thr  
 195 200 205  
 Ser Ser Ser Lys Gly Tyr Asn Leu Phe Leu Val Ala Ala His Glu Phe  
 210 215 220  
 Gly His Ser Leu Gly Leu Asp His Ser Lys Asp Pro Gly Ala Leu Met  
 225 230 235 240  
 Phe Pro Ile Tyr Thr Thr Gly Lys Ser His Phe Met Leu Pro Asp  
 245 250 255  
 Asp Asp Val Gln Gly Ile Gln Ser Leu Tyr Gly Pro Gly Asp Glu Asp  
 260 265 270  
 Pro Asn Pro Lys His Pro Lys Thr Pro Asp Lys Cys Asp Pro Ser Leu

275                      280                      285  
 Ser Leu Asp Ala Ile Thr Ser Leu Arg Gly Glu Thr Met Ile Phe Lys  
 290                      295                      300  
 Asp Arg Phe Phe Trp Arg Leu His Pro Gln Gln Val Asp Ala Glu Leu  
 305                      310                      315                      320  
 Phe Leu Thr Lys Ser Phe Trp Pro Glu Leu Pro Asn Arg Ile Asp Ala  
 325                      330                      335  
 Ala Tyr Glu His Pro Ser His Asp Leu Ile Phe Ile Phe Arg Gly Arg  
 340                      345                      350  
 Lys Phe Trp Ala Leu Asn Gly Tyr Asp Ile Leu Glu Gly Tyr Pro Lys  
 355                      360                      365  
 Lys Ile Ser Glu Leu Gly Leu Pro Lys Glu Val Lys Lys Ile Ser Ala  
 370                      375                      380  
 Ala Val His Phe Glu Asp Thr Gly Lys Thr Leu Leu Phe Ser Gly Asn  
 385                      390                      395                      400  
 Gln Val Trp Arg Tyr Asp Asp Thr Asn His Ile Met Asp Lys Asp Tyr  
 405                      410                      415  
 Pro Arg Leu Ile Glu Glu Asp Phe Pro Gly Ile Gly Asp Lys Val Asp  
 420                      425                      430  
 Ala Val Tyr Glu Lys Asn Gly Tyr Ile Tyr Phe Phe Asn Gly Pro Ile  
 435                      440                      445  
 Gln Phe Glu Tyr Ser Ile Trp Ser Asn Arg Ile Val Arg Val Met Pro  
 450                      455                      460  
 Ala Asn Ser Ile Leu Trp Cys  
 465                      470

&lt;210&gt; 22

&lt;211&gt; 267

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 22

Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu  
 1                      5                      10                      15  
 Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp  
 20                      25                      30  
 Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu  
 35                      40                      45  
 Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys  
 50                      55                      60  
 Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu  
 65                      70                      75                      80  
 Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser  
 85                      90                      95  
 Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg  
 100                      105                      110  
 Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu  
 115                      120                      125  
 Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe  
 130                      135                      140  
 Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg  
 145                      150                      155                      160  
 Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu  
 165                      170                      175  
 Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe  
 180                      185                      190  
 Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe  
 195                      200                      205



14

Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His  
 210 215 220  
 Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp  
 225 230 235 240  
 Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys  
 245 250 255  
 Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys  
 260 265

<210> 23  
 <211> 470  
 <212> PRT  
 <213> Homo sapiens

<400> 23  
 Met Lys Phe Leu Leu Ile Leu Leu Leu Gln Ala Thr Ala Ser Gly Ala  
 1 5 10 15  
 Leu Pro Leu Asn Ser Ser Thr Ser Leu Glu Lys Asn Asn Val Leu Phe  
 20 25 30  
 Gly Glu Arg Tyr Leu Glu Lys Phe Tyr Gly Leu Glu Ile Asn Lys Leu  
 35 40 45  
 Pro Val Thr Lys Met Lys Tyr Ser Gly Asn Leu Met Lys Glu Lys Ile  
 50 55 60  
 Gln Glu Met Gln His Phe Leu Gly Leu Lys Val Thr Gly Gln Leu Asp  
 65 70 75 80  
 Thr Ser Thr Leu Glu Met Met His Ala Pro Arg Cys Gly Val Pro Asp  
 85 90 95  
 Val His His Phe Arg Glu Met Pro Gly Gly Pro Val Trp Arg Lys His  
 100 105 110  
 Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr Thr Pro Asp Met Asn Arg Glu  
 115 120 125  
 Asp Val Asp Tyr Ala Ile Arg Lys Ala Phe Gln Val Trp Ser Asn Val  
 130 135 140  
 Thr Pro Leu Lys Phe Ser Lys Ile Asn Thr Gly Met Ala Asp Ile Leu  
 145 150 155 160  
 Val Val Phe Ala Arg Gly Ala His Gly Asp Phe His Ala Phe Asp Gly  
 165 170 175  
 Lys Gly Gly Ile Leu Ala His Ala Phe Gly Pro Gly Ser Gly Ile Gly  
 180 185 190  
 Gly Asp Ala His Phe Asp Glu Asp Glu Phe Trp Thr Thr His Ser Gly  
 195 200 205  
 Gly Thr Asn Leu Phe Leu Thr Ala Val His Glu Ile Gly His Ser Leu  
 210 215 220  
 Gly Leu Gly His Ser Ser Asp Pro Lys Ala Val Met Phe Pro Thr Tyr  
 225 230 235 240  
 Lys Tyr Val Asp Ile Asn Thr Phe Arg Leu Ser Ala Asp Asp Ile Arg  
 245 250 255  
 Gly Ile Gln Ser Leu Tyr Gly Asp Pro Lys Glu Asn Gln Arg Leu Pro  
 260 265 270  
 Asn Pro Asp Asn Ser Glu Pro Ala Leu Cys Asp Pro Asn Leu Ser Phe  
 275 280 285  
 Asp Ala Val Thr Thr Val Gly Asn Lys Ile Phe Phe Phe Lys Asp Arg  
 290 295 300  
 Phe Phe Trp Leu Lys Val Ser Glu Arg Pro Lys Thr Ser Val Asn Leu  
 305 310 315 320  
 Ile Ser Ser Leu Trp Pro Thr Leu Pro Ser Gly Ile Glu Ala Ala Tyr  
 325 330 335  
 Glu Ile Glu Ala Arg Asn Gln Val Phe Leu Phe Lys Asp Asp Lys Tyr

340 345 350  
 Trp Leu Ile Ser Asn Leu Arg Pro Glu Pro Asn Tyr Pro Lys Ser Ile  
 355 360 365  
 His Ser Phe Gly Phe Pro Asn Phe Val Lys Lys Ile Asp Ala Ala Val  
 370 375 380  
 Phe Asn Pro Arg Phe Tyr Arg Thr Tyr Phe Phe Val Asp Asn Gln Tyr  
 385 390 395 400  
 Trp Arg Tyr Asp Glu Arg Arg Gln Met Met Asp Pro Gly Tyr Pro Lys  
 405 410 415  
 Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val  
 420 425 430  
 Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln  
 435 440 445  
 Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser  
 450 455 460  
 Asn Ser Trp Phe Gly Cys  
 465 470

<210> 24  
 <211> 477  
 <212> PRT  
 <213> Homo sapiens

<400> 24  
 Met Lys Ser Leu Pro Ile Leu Leu Leu Leu Cys Val Ala Val Cys Ser  
 1 5 10 15  
 Ala Tyr Pro Leu Asp Gly Ala Ala Arg Gly Glu Asp Thr Ser Met Asn  
 20 25 30  
 Leu Val Gln Lys Tyr Leu Glu Asn Tyr Tyr Asp Leu Lys Lys Asp Val  
 35 40 45  
 Lys Gln Phe Val Arg Arg Lys Asp Ser Gly Pro Val Val Lys Lys Ile  
 50 55 60  
 Arg Glu Met Gln Lys Phe Leu Gly Leu Glu Val Thr Gly Lys Leu Asp  
 65 70 75 80  
 Ser Asp Thr Leu Glu Val Met Arg Lys Pro Arg Cys Gly Val Pro Asp  
 85 90 95  
 Val Gly His Phe Arg Thr Phe Pro Gly Ile Pro Lys Trp Arg Lys Thr  
 100 105 110  
 His Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp Leu Pro Lys Asp  
 115 120 125  
 Ala Val Asp Ser Ala Val Glu Lys Ala Leu Lys Val Trp Glu Glu Val  
 130 135 140  
 Thr Pro Leu Thr Phe Ser Arg Leu Tyr Glu Gly Glu Ala Asp Ile Met  
 145 150 155 160  
 Ile Ser Phe Ala Val Arg Glu His Gly Asp Phe Tyr Pro Phe Asp Gly  
 165 170 175  
 Pro Gly Asn Val Leu Ala His Ala Tyr Ala Pro Gly Pro Gly Ile Asn  
 180 185 190  
 Gly Asp Ala His Phe Asp Asp Asp Glu Gln Trp Thr Lys Asp Thr Thr  
 195 200 205  
 Gly Thr Asn Leu Phe Leu Val Ala Ala His Glu Ile Gly His Ser Leu  
 210 215 220  
 Gly Leu Phe His Ser Ala Asn Thr Glu Ala Leu Met Tyr Pro Leu Tyr  
 225 230 235 240  
 His Ser Leu Thr Asp Leu Thr Arg Phe Arg Leu Ser Gln Asp Asp Ile  
 245 250 255  
 Asn Gly Ile Gln Ser Leu Tyr Gly Pro Pro Pro Asp Ser Pro Glu Thr  
 260 265 270

Pro Leu Val Pro Thr Glu Pro Val Pro Pro Glu Pro Gly Thr Pro Ala  
 275 280 285  
 Asn Cys Asp Pro Ala Leu Ser Phe Asp Ala Val Ser Thr Leu Arg Gly  
 290 295 300  
 Glu Ile Leu Ile Phe Lys Asp Arg His Phe Trp Arg Lys Ser Leu Arg  
 305 310 315 320  
 Lys Leu Glu Pro Glu Leu His Leu Ile Ser Ser Phe Trp Pro Ser Leu  
 325 330 335  
 Pro Ser Gly Val Asp Ala Ala Tyr Glu Val Thr Ser Lys Asp Leu Val  
 340 345 350  
 Phe Ile Phe Lys Gly Asn Gln Phe Trp Ala Ile Arg Gly Asn Glu Val  
 355 360 365  
 Arg Ala Gly Tyr Pro Arg Gly Ile His Thr Leu Gly Phe Pro Pro Thr  
 370 375 380  
 Val Arg Lys Ile Asp Ala Ala Ile Ser Asp Lys Glu Lys Asn Lys Thr  
 385 390 395 400  
 Tyr Phe Phe Val Glu Asp Lys Tyr Trp Arg Phe Asp Glu Lys Arg Asn  
 405 410 415  
 Ser Met Glu Pro Gly Phe Pro Lys Gln Ile Ala Glu Asp Phe Pro Gly  
 420 425 430  
 Ile Asp Ser Lys Ile Asp Ala Val Phe Glu Glu Phe Gly Phe Phe Tyr  
 435 440 445  
 Phe Phe Thr Gly Ser Ser Gln Leu Glu Phe Asp Pro Asn Ala Lys Lys  
 450 455 460  
 Val Thr His Thr Leu Lys Ser Asn Ser Trp Leu Asn Cys  
 465 470 475

<210> 25

<211> 476

<212> PRT

<213> Homo sapiens

<400> 25

Met Met His Leu Ala Phe Leu Val Leu Leu Cys Leu Pro Val Cys Ser  
 1 5 10 15  
 Ala Tyr Pro Leu Ser Gly Ala Ala Lys Glu Glu Asp Ser Asn Lys Asp  
 20 25 30  
 Leu Ala Gln Gln Tyr Leu Glu Lys Tyr Tyr Asn Leu Glu Lys Asp Val  
 35 40 45  
 Lys Gln Phe Arg Arg Lys Asp Ser Asn Leu Ile Val Lys Lys Ile Gln  
 50 55 60  
 Gly Met Gln Lys Phe Leu Gly Leu Glu Val Thr Gly Lys Leu Asp Thr  
 65 70 75 80  
 Asp Thr Leu Glu Val Met Arg Lys Pro Arg Cys Gly Val Pro Asp Val  
 85 90 95  
 Gly His Phe Ser Ser Phe Pro Gly Met Pro Lys Trp Arg Lys Thr His  
 100 105 110  
 Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp Leu Pro Arg Asp Ala  
 115 120 125  
 Val Asp Ser Ala Ile Glu Lys Ala Leu Lys Val Trp Glu Glu Val Thr  
 130 135 140  
 Pro Leu Thr Phe Ser Arg Leu Tyr Glu Gly Glu Ala Asp Ile Met Ile  
 145 150 155 160  
 Ser Phe Ala Val Lys Glu His Gly Asp Phe Tyr Ser Phe Asp Gly Pro  
 165 170 175  
 Gly His Ser Leu Ala His Ala Tyr Pro Pro Gly Pro Gly Leu Tyr Gly  
 180 185 190  
 Asp Ile His Phe Asp Asp Asp Glu Lys Trp Thr Glu Asp Ala Ser Gly

195                      200                      205  
 Thr Asn Leu Phe Leu Val Ala Ala His Glu Leu Gly His Ser Leu Gly  
 210                      215                      220  
 Leu Phe His Ser Ala Asn Thr Glu Ala Leu Met Tyr Pro Leu Tyr Asn  
 225                      230                      235                      240  
 Ser Phe Thr Glu Leu Ala Gln Phe Arg Leu Ser Gln Asp Asp Val Asn  
 245                      250                      255  
 Gly Ile Gln Ser Leu Tyr Gly Pro Pro Pro Ala Ser Thr Glu Glu Pro  
 260                      265                      270  
 Leu Val Pro Thr Lys Ser Val Pro Ser Gly Ser Glu Met Pro Ala Lys  
 275                      280                      285  
 Cys Asp Pro Ala Leu Ser Phe Asp Ala Ile Ser Thr Leu Arg Gly Glu  
 290                      295                      300  
 Tyr Leu Phe Phe Lys Asp Arg Tyr Phe Trp Arg Arg Ser His Trp Asn  
 305                      310                      315                      320  
 Pro Glu Pro Glu Phe His Leu Ile Ser Ala Phe Trp Pro Ser Leu Pro  
 325                      330                      335  
 Ser Tyr Leu Asp Ala Ala Tyr Glu Val Asn Ser Arg Asp Thr Val Phe  
 340                      345                      350  
 Ile Phe Lys Gly Asn Glu Phe Trp Ala Ile Arg Gly Asn Glu Val Gln  
 355                      360                      365  
 Ala Gly Tyr Pro Arg Gly Ile His Thr Leu Gly Phe Pro Pro Thr Ile  
 370                      375                      380  
 Arg Lys Ile Asp Ala Ala Val Ser Asp Lys Glu Lys Lys Lys Thr Tyr  
 385                      390                      395                      400  
 Phe Phe Ala Ala Asp Lys Tyr Trp Arg Phe Asp Glu Asn Ser Gln Ser  
 405                      410                      415  
 Met Glu Gln Gly Phe Pro Arg Leu Ile Ala Asp Asp Phe Pro Gly Val  
 420                      425                      430  
 Glu Pro Lys Val Asp Ala Val Leu Gln Ala Phe Gly Phe Phe Tyr Phe  
 435                      440                      445  
 Phe Ser Gly Ser Ser Gln Phe Glu Phe Asp Pro Asn Ala Arg Met Val  
 450                      455                      460  
 Thr His Ile Leu Lys Ser Asn Ser Trp Leu His Cys  
 465                      470                      475

&lt;210&gt; 26

&lt;211&gt; 488

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 26

Met Ala Pro Ala Ala Trp Leu Arg Ser Ala Ala Ala Arg Ala Leu Leu  
 1                      5                      10                      15  
 Pro Pro Met Leu Leu Leu Leu Leu Gln Pro Pro Pro Leu Leu Ala Arg  
 20                      25                      30  
 Ala Leu Pro Pro Asp Val His His Leu His Ala Glu Arg Arg Gly Pro  
 35                      40                      45  
 Gln Pro Trp His Ala Ala Leu Pro Ser Ser Pro Ala Pro Ala Pro Ala  
 50                      55                      60  
 Thr Gln Glu Ala Pro Arg Pro Ala Ser Ser Leu Arg Pro Pro Arg Cys  
 65                      70                      75                      80  
 Gly Val Pro Asp Pro Ser Asp Gly Leu Ser Ala Arg Asn Arg Gln Lys  
 85                      90                      95  
 Arg Phe Val Leu Ser Gly Gly Arg Trp Glu Lys Thr Asp Leu Thr Tyr  
 100                      105                      110  
 Arg Ile Leu Arg Phe Pro Trp Gln Leu Val Gln Glu Gln Val Arg Gln  
 115                      120                      125

Thr Met Ala Glu Ala Leu Lys Val Trp Ser Asp Val Thr Pro Leu Thr  
 130 135 140  
 Phe Thr Glu Val His Glu Gly Arg Ala Asp Ile Met Ile Asp Phe Ala  
 145 150 155 160  
 Arg Tyr Trp Asp Gly Asp Asp Leu Pro Phe Asp Gly Pro Gly Gly Ile  
 165 170 175  
 Leu Ala His Ala Phe Phe Pro Lys Thr His Arg Glu Gly Asp Val His  
 180 185 190  
 Phe Asp Tyr Asp Glu Thr Trp Thr Ile Gly Asp Asp Gln Gly Thr Asp  
 195 200 205  
 Leu Leu Gln Val Ala Ala His Glu Phe Gly His Val Leu Gly Leu Gln  
 210 215 220  
 His Thr Thr Ala Ala Lys Ala Leu Met Ser Ala Phe Tyr Thr Phe Arg  
 225 230 235 240  
 Tyr Pro Leu Ser Leu Ser Pro Asp Asp Cys Arg Gly Val Gln His Leu  
 245 250 255  
 Tyr Gly Gln Pro Trp Pro Thr Val Thr Ser Arg Thr Pro Ala Leu Gly  
 260 265 270  
 Pro Gln Ala Gly Ile Asp Thr Asn Glu Ile Ala Pro Leu Glu Pro Asp  
 275 280 285  
 Ala Pro Pro Asp Ala Cys Glu Ala Ser Phe Asp Ala Val Ser Thr Ile  
 290 295 300  
 Arg Gly Glu Leu Phe Phe Phe Lys Ala Gly Phe Val Trp Arg Leu Arg  
 305 310 315 320  
 Gly Gly Gln Leu Gln Pro Gly Tyr Pro Ala Leu Ala Ser Arg His Trp  
 325 330 335  
 Gln Gly Leu Pro Ser Pro Val Asp Ala Ala Phe Glu Asp Ala Gln Gly  
 340 345 350  
 His Ile Trp Phe Phe Gln Gly Ala Gln Tyr Trp Val Tyr Asp Gly Glu  
 355 360 365  
 Lys Pro Val Leu Gly Pro Ala Pro Leu Thr Glu Leu Gly Leu Val Arg  
 370 375 380  
 Phe Pro Val His Ala Ala Leu Val Trp Gly Pro Glu Lys Asn Lys Ile  
 385 390 395 400  
 Tyr Phe Phe Arg Gly Arg Asp Tyr Trp Arg Phe His Pro Ser Thr Arg  
 405 410 415  
 Arg Val Asp Ser Pro Val Pro Arg Arg Ala Thr Asp Trp Arg Gly Val  
 420 425 430  
 Pro Ser Glu Ile Asp Ala Ala Phe Gln Asp Ala Asp Gly Tyr Ala Tyr  
 435 440 445  
 Phe Leu Arg Gly Arg Leu Tyr Trp Lys Phe Asp Pro Val Lys Val Lys  
 450 455 460  
 Ala Leu Glu Gly Phe Pro Arg Leu Val Gly Pro Asp Phe Phe Gly Cys  
 465 470 475 480  
 Ala Glu Pro Ala Asn Thr Phe Leu  
 485

&lt;210&gt; 27

&lt;211&gt; 582

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 27

Met Ser Pro Ala Pro Arg Pro Ser Arg Cys Leu Leu Leu Pro Leu Leu  
 1 5 10 15  
 Thr Leu Gly Thr Ala Leu Ala Ser Leu Gly Ser Ala Gln Ser Ser Ser  
 20 25 30  
 Phe Ser Pro Glu Ala Trp Leu Gln Gln Tyr Gly Tyr Leu Pro Pro Gly

Pro Arg Arg Pro Gly Arg Pro Asp His Arg Pro Pro Arg Pro Pro Gln  
 325 330 335  
 Pro Pro Pro Pro Gly Gly Lys Pro Glu Arg Pro Pro Lys Pro Gly Pro  
 340 345 350  
 Pro Val Gln Pro Arg Ala Thr Glu Arg Pro Asp Gln Tyr Gly Pro Asn  
 355 360 365  
 Ile Cys Asp Gly Asp Phe Asp Thr Val Ala Met Leu Arg Gly Glu Met  
 370 375 380  
 Phe Val Phe Lys Gly Arg Trp Phe Trp Arg Val Arg His Asn Arg Val  
 385 390 395 400  
 Leu Asp Asn Tyr Pro Met Pro Ile Gly His Phe Trp Arg Gly Leu Pro  
 405 410 415  
 Gly Asp Ile Ser Ala Ala Tyr Glu Arg Gln Asp Gly Arg Phe Val Phe  
 420 425 430  
 Phe Lys Gly Asp Arg Tyr Trp Leu Phe Arg Glu Ala Asn Leu Glu Pro  
 435 440 445  
 Gly Tyr Pro Gln Pro Leu Thr Ser Tyr Gly Leu Gly Ile Pro Tyr Asp  
 450 455 460  
 Arg Ile Asp Thr Ala Ile Trp Trp Glu Pro Thr Gly His Thr Phe Phe  
 465 470 475 480  
 Phe Gln Glu Asp Arg Tyr Trp Arg Phe Asn Glu Glu Thr Gln Arg Gly  
 485 490 495  
 Asp Pro Gly Tyr Pro Lys Pro Ile Ser Val Trp Gln Gly Ile Pro Ala  
 500 505 510  
 Ser Pro Lys Gly Ala Phe Leu Ser Asn Asp Ala Ala Tyr Thr Tyr Phe  
 515 520 525  
 Tyr Lys Gly Thr Lys Tyr Trp Lys Phe Asp Asn Glu Arg Leu Arg Met  
 530 535 540  
 Glu Pro Gly Tyr Pro Lys Ser Ile Leu Arg Asp Phe Met Gly Cys Gln  
 545 550 555 560  
 Glu His Val Glu Pro Gly Pro Arg Trp Pro Asp Val Ala Arg Pro Pro  
 565 570 575  
 Phe Asn Pro His Gly Gly Ala Glu Pro Gly Ala Asp Ser Ala Glu Gly  
 580 585 590  
 Asp Val Gly Asp Gly Asp Gly Asp Phe Gly Ala Gly Val Asn Lys Asp  
 595 600 605  
 Gly Gly Ser Arg Val Val Val Gln Met Glu Glu Val Ala Arg Thr Val  
 610 615 620  
 Asn Val Val Met Val Leu Val Pro Leu Leu Leu Leu Cys Val Leu  
 625 630 635 640  
 Gly Leu Thr Tyr Ala Leu Val Gln Met Gln Arg Lys Gly Ala Pro Arg  
 645 650 655  
 Val Leu Leu Tyr Cys Lys Arg Ser Leu Gln Glu Trp Val  
 660 665

&lt;210&gt; 29

&lt;211&gt; 607

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 29

Met Ile Leu Leu Thr Phe Ser Thr Gly Arg Arg Leu Asp Phe Val His  
 1 5 10 15  
 His Ser Gly Val Phe Phe Leu Gln Thr Leu Leu Trp Ile Leu Cys Ala  
 20 25 30  
 Thr Val Cys Gly Thr Glu Gln Tyr Phe Asn Val Glu Val Trp Leu Gln  
 35 40 45  
 Lys Tyr Gly Tyr Leu Pro Pro Thr Asp Pro Arg Met Ser Val Leu Arg

50 55 60  
 Ser Ala Glu Thr Met Gln Ser Ala Leu Ala Ala Met Gln Gln Phe Tyr  
 65 70 75 80  
 Gly Ile Asn Met Thr Gly Lys Val Asp Arg Asn Thr Ile Asp Trp Met  
 85 90 95  
 Lys Lys Pro Arg Cys Gly Val Pro Asp Gln Thr Arg Gly Ser Ser Lys  
 100 105 110  
 Phe His Ile Arg Arg Lys Arg Tyr Ala Leu Thr Gly Gln Lys Trp Gln  
 115 120 125  
 His Lys His Ile Thr Tyr Ser Ile Lys Asn Val Thr Pro Lys Val Gly  
 130 135 140  
 Asp Pro Glu Thr Arg Lys Ala Ile Arg Arg Ala Phe Asp Val Trp Gln  
 145 150 155 160  
 Asn Val Thr Pro Leu Thr Phe Glu Glu Val Pro Tyr Ser Glu Leu Glu  
 165 170 175  
 Asn Gly Lys Arg Asp Val Asp Ile Thr Ile Ile Phe Ala Ser Gly Phe  
 180 185 190  
 His Gly Asp Ser Ser Pro Phe Asp Gly Glu Gly Gly Phe Leu Ala His  
 195 200 205  
 Ala Tyr Phe Pro Gly Pro Gly Ile Gly Gly Asp Thr His Phe Asp Ser  
 210 215 220  
 Asp Glu Pro Trp Thr Leu Gly Asn Pro Asn His Asp Gly Asn Asp Leu  
 225 230 235 240  
 Phe Leu Val Ala Val His Glu Leu Gly His Ala Leu Gly Leu Glu His  
 245 250 255  
 Ser Asn Asp Pro Thr Ala Ile Met Ala Pro Phe Tyr Gln Tyr Met Glu  
 260 265 270  
 Thr Asp Asn Phe Lys Leu Pro Asn Asp Asp Leu Gln Gly Ile Gln Lys  
 275 280 285  
 Ile Tyr Gly Pro Pro Asp Lys Ile Pro Pro Pro Thr Arg Pro Leu Pro  
 290 295 300  
 Thr Val Pro Pro His Arg Ser Ile Pro Pro Ala Asp Pro Arg Lys Asn  
 305 310 315 320  
 Asp Arg Pro Lys Pro Pro Arg Pro Pro Thr Gly Arg Pro Ser Tyr Pro  
 325 330 335  
 Gly Ala Lys Pro Asn Ile Cys Asp Gly Asn Phe Asn Thr Leu Ala Ile  
 340 345 350  
 Leu Arg Arg Glu Met Phe Val Phe Lys Asp Gln Trp Phe Trp Arg Val  
 355 360 365  
 Arg Asn Asn Arg Val Met Asp Gly Tyr Pro Met Gln Ile Thr Tyr Phe  
 370 375 380  
 Trp Arg Gly Leu Pro Pro Ser Ile Asp Ala Val Tyr Glu Asn Ser Asp  
 385 390 395 400  
 Gly Asn Phe Val Phe Phe Lys Gly Asn Lys Tyr Trp Val Phe Lys Asp  
 405 410 415  
 Thr Thr Leu Gln Pro Gly Tyr Pro His Asp Leu Ile Thr Leu Gly Ser  
 420 425 430  
 Gly Ile Pro Pro His Gly Ile Asp Ser Ala Ile Trp Trp Glu Asp Val  
 435 440 445  
 Gly Lys Thr Tyr Phe Phe Lys Gly Asp Arg Tyr Trp Arg Tyr Ser Glu  
 450 455 460  
 Glu Met Lys Thr Met Asp Pro Gly Tyr Pro Lys Pro Ile Thr Val Trp  
 465 470 475 480  
 Lys Gly Ile Pro Glu Ser Pro Gln Gly Ala Phe Val His Lys Glu Asn  
 485 490 495  
 Gly Phe Thr Tyr Phe Tyr Lys Gly Lys Glu Tyr Trp Lys Phe Asn Asn  
 500 505 510  
 Gln Ile Leu Lys Val Glu Pro Gly Tyr Pro Arg Ser Ile Leu Lys Asp

515                      520                      525  
 Phe Met Gly Cys Asp Gly Pro Thr Asp Arg Val Lys Glu Gly His Ser  
 530                      535                      540  
 Pro Pro Asp Asp Val Asp Ile Val Ile Lys Leu Asp Asn Thr Ala Ser  
 545                      550                      555                      560  
 Thr Val Lys Ala Ile Ala Ile Val Ile Pro Cys Ile Leu Ala Leu Cys  
 565                      570                      575  
 Leu Leu Val Leu Val Tyr Thr Val Phe Gln Phe Lys Arg Lys Gly Thr  
 580                      585                      590  
 Pro Arg His Ile Leu Tyr Cys Lys Arg Ser Met Gln Glu Trp Val  
 595                      600                      605

&lt;210&gt; 30

&lt;211&gt; 519

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

Met Gln Gln Phe Gly Gly Leu Glu Ala Thr Gly Ile Leu Asp Glu Ala  
 1                      5                      10                      15  
 Thr Leu Ala Leu Met Lys Thr Pro Arg Cys Ser Leu Pro Asp Leu Pro  
 20                      25                      30  
 Val Leu Thr Gln Ala Arg Arg Arg Arg Gln Ala Pro Ala Pro Thr Lys  
 35                      40                      45  
 Trp Asn Lys Arg Asn Leu Ser Trp Arg Val Arg Thr Phe Pro Arg Asp  
 50                      55                      60  
 Ser Pro Leu Gly His Asp Thr Val Arg Ala Leu Met Tyr Tyr Ala Leu  
 65                      70                      75                      80  
 Lys Val Trp Ser Asp Ile Ala Pro Leu Asn Phe His Glu Val Ala Gly  
 85                      90                      95  
 Ser Thr Ala Asp Ile Gln Ile Asp Phe Ser Lys Ala Asp His Asn Asp  
 100                      105                      110  
 Gly Tyr Pro Phe Asp Gly Pro Gly Gly Thr Val Ala His Ala Phe Phe  
 115                      120                      125  
 Pro Gly His His His Thr Ala Gly Asp Thr His Phe Asp Asp Asp Glu  
 130                      135                      140  
 Ala Trp Thr Phe Arg Ser Ser Asp Ala His Gly Met Asp Leu Phe Ala  
 145                      150                      155                      160  
 Val Ala Val His Glu Phe Gly His Ala Ile Gly Leu Ser His Val Ala  
 165                      170                      175  
 Ala Ala His Ser Ile Met Arg Pro Tyr Tyr Gln Gly Pro Val Gly Asp  
 180                      185                      190  
 Pro Leu Arg Tyr Gly Leu Pro Tyr Glu Asp Lys Val Arg Val Trp Gln  
 195                      200                      205  
 Leu Tyr Gly Val Arg Glu Ser Val Ser Pro Thr Ala Gln Pro Glu Glu  
 210                      215                      220  
 Pro Pro Leu Leu Pro Glu Pro Pro Asp Asn Arg Ser Ser Ala Pro Pro  
 225                      230                      235                      240  
 Arg Lys Asp Val Pro His Arg Cys Ser Thr His Phe Asp Ala Val Ala  
 245                      250                      255  
 Gln Ile Arg Gly Glu Ala Phe Phe Phe Lys Gly Lys Tyr Phe Trp Arg  
 260                      265                      270  
 Leu Thr Arg Asp Arg His Leu Val Ser Leu Gln Pro Ala Gln Met His  
 275                      280                      285  
 Arg Phe Trp Arg Gly Leu Pro Leu His Leu Asp Ser Val Asp Ala Val  
 290                      295                      300  
 Tyr Glu Arg Thr Ser Asp His Lys Ile Val Phe Phe Lys Gly Asp Arg  
 305                      310                      315                      320



Tyr Trp Val Phe Lys Asp Asn Asn Val Glu Glu Gly Tyr Pro Arg Pro  
325 330 335  
Val Ser Asp Phe Ser Leu Pro Pro Gly Gly Ile Asp Ala Ala Phe Ser  
340 345 350  
Trp Ala His Asn Asp Arg Thr Tyr Phe Phe Lys Asp Gln Leu Tyr Trp  
355 360 365  
Arg Tyr Asp Asp His Thr Arg His Met Asp Pro Gly Tyr Pro Ala Gln  
370 375 380  
Ser Pro Leu Trp Arg Gly Val Pro Ser Thr Leu Asp Asp Ala Met Arg  
385 390 395 400  
Trp Ser Asp Gly Ala Ser Tyr Phe Phe Arg Gly Gln Glu Tyr Trp Lys  
405 410 415  
Val Leu Asp Gly Glu Leu Glu Val Ala Pro Gly Tyr Pro Gln Ser Thr  
420 425 430  
Ala Arg Asp Trp Leu Val Cys Gly Asp Ser Gln Ala Asp Gly Ser Val  
435 440 445  
Ala Ala Gly Val Asp Ala Ala Glu Gly Pro Arg Ala Pro Pro Gly Gln  
450 455 460  
His Asp Gln Ser Arg Ser Glu Asp Gly Tyr Glu Val Cys Ser Cys Thr  
465 470 475 480  
Ser Gly Ala Ser Ser Pro Pro Gly Ala Pro Gly Pro Leu Val Ala Ala  
485 490 495  
Thr Met Leu Leu Leu Leu Pro Pro Leu Ser Pro Gly Ala Leu Trp Thr  
500 505 510  
Ala Ala Gln Ala Leu Thr Leu  
515

&lt;210&gt; 31

&lt;211&gt; 508

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 31

Met Asn Cys Gln Gln Leu Trp Leu Gly Phe Leu Leu Pro Met Thr Val  
1 5 10 15  
Ser Gly Arg Val Leu Gly Leu Ala Glu Val Ala Pro Val Asp Tyr Leu  
20 25 30  
Ser Gln Tyr Gly Tyr Leu Gln Lys Pro Leu Glu Gly Ser Asn Asn Phe  
35 40 45  
Lys Pro Glu Asp Ile Thr Glu Ala Leu Arg Ala Phe Gln Glu Ala Ser  
50 55 60  
Glu Leu Pro Val Ser Gly Gln Leu Asp Asp Ala Thr Arg Ala Arg Met  
65 70 75 80  
Arg Gln Pro Arg Cys Gly Leu Glu Asp Pro Phe Asn Gln Lys Thr Leu  
85 90 95  
Lys Tyr Leu Leu Leu Gly Arg Trp Arg Lys Lys His Leu Thr Phe Arg  
100 105 110  
Ile Leu Asn Leu Pro Ser Thr Leu Pro Pro His Thr Ala Arg Ala Ala  
115 120 125  
Leu Arg Gln Ala Phe Gln Asp Trp Ser Asn Val Ala Pro Leu Thr Phe  
130 135 140  
Gln Glu Val Gln Ala Gly Ala Ala Asp Ile Arg Leu Ser Phe His Gly  
145 150 155 160  
Arg Gln Ser Ser Tyr Cys Ser Asn Thr Phe Asp Gly Pro Gly Arg Val  
165 170 175  
Leu Ala His Ala Asp Ile Pro Glu Leu Gly Ser Val His Phe Asp Glu  
180 185 190  
Asp Glu Phe Trp Thr Glu Gly Thr Tyr Arg Gly Val Asn Leu Arg Ile

195 200 205  
 Ile Ala Ala His Glu Val Gly His Ala Leu Gly Leu Gly His Ser Arg  
 210 215 220  
 Tyr Ser Gln Ala Leu Met Ala Pro Val Tyr Glu Gly Tyr Arg Pro His  
 225 230 235 240  
 Phe Lys Leu His Pro Asp Asp Val Ala Gly Ile Gln Ala Leu Tyr Gly  
 245 250 255  
 Lys Lys Ser Pro Val Ile Arg Asp Glu Glu Glu Glu Thr Glu Leu  
 260 265 270  
 Pro Thr Val Pro Pro Val Pro Thr Glu Pro Ser Pro Met Pro Asp Pro  
 275 280 285  
 Cys Ser Ser Glu Leu Asp Ala Met Met Leu Gly Pro Arg Gly Lys Thr  
 290 295 300  
 Tyr Ala Phe Lys Gly Asp Tyr Val Trp Thr Val Ser Asp Ser Gly Pro  
 305 310 315 320  
 Gly Pro Leu Phe Arg Val Ser Ala Leu Trp Glu Gly Leu Pro Gly Asn  
 325 330 335  
 Leu Asp Ala Ala Val Tyr Ser Pro Arg Thr Gln Trp Ile His Phe Phe  
 340 345 350  
 Lys Gly Asp Lys Val Trp Arg Tyr Ile Asn Phe Lys Met Ser Pro Gly  
 355 360 365  
 Phe Pro Lys Lys Leu Asn Arg Val Glu Pro Asn Leu Asp Ala Ala Leu  
 370 375 380  
 Tyr Trp Pro Leu Asn Gln Lys Val Phe Leu Phe Lys Gly Ser Gly Tyr  
 385 390 395 400  
 Trp Gln Trp Asp Glu Leu Ala Arg Thr Asp Phe Ser Ser Tyr Pro Lys  
 405 410 415  
 Pro Ile Lys Gly Leu Phe Thr Gly Val Pro Asn Gln Pro Ser Ala Ala  
 420 425 430  
 Met Ser Trp Gln Asp Gly Arg Val Tyr Phe Phe Lys Gly Lys Val Tyr  
 435 440 445  
 Trp Arg Leu Asn Gln Gln Leu Arg Val Glu Lys Gly Tyr Pro Arg Asn  
 450 455 460  
 Ile Ser His Asn Trp Met His Cys Arg Pro Arg Thr Ile Asp Thr Thr  
 465 470 475 480  
 Pro Ser Gly Gly Asn Thr Thr Pro Ser Gly Thr Gly Ile Thr Leu Asp  
 485 490 495  
 Thr Thr Leu Ser Ala Thr Glu Thr Thr Phe Glu Tyr  
 500 505

&lt;210&gt; 32

&lt;211&gt; 471

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 32

Met His Pro Gly Val Leu Ala Ala Phe Leu Phe Leu Ser Trp Thr His  
 1 5 10 15  
 Cys Arg Ala Leu Pro Leu Pro Ser Gly Gly Asp Glu Asp Asp Leu Ser  
 20 25 30  
 Glu Glu Asp Leu Gln Phe Ala Glu Arg Tyr Leu Arg Ser Tyr Tyr His  
 35 40 45  
 Pro Thr Asn Leu Ala Gly Ile Leu Lys Glu Asn Ala Ala Ser Ser Met  
 50 55 60  
 Thr Glu Arg Leu Arg Glu Met Gln Ser Phe Phe Gly Leu Glu Val Thr  
 65 70 75 80  
 Gly Lys Leu Asp Asp Asn Thr Leu Asp Val Met Lys Lys Pro Arg Cys  
 85 90 95

Gly Val Pro Asp Val Gly Glu Tyr Asn Val Phe Pro Arg Thr Leu Lys  
 100 105 110  
 Trp Ser Lys Met Asn Leu Thr Tyr Arg Ile Val Asn Tyr Thr Pro Asp  
 115 120 125  
 Met Thr His Ser Glu Val Glu Lys Ala Phe Lys Lys Ala Phe Lys Val  
 130 135 140  
 Trp Ser Asp Val Thr Pro Leu Asn Phe Thr Arg Leu His Asp Gly Ile  
 145 150 155 160  
 Ala Asp Ile Met Ile Ser Phe Gly Ile Lys Glu His Gly Asp Phe Tyr  
 165 170 175  
 Pro Phe Asp Gly Pro Ser Gly Leu Leu Ala His Ala Phe Pro Pro Gly  
 180 185 190  
 Pro Asn Tyr Gly Gly Asp Ala His Phe Asp Asp Asp Glu Thr Trp Thr  
 195 200 205  
 Ser Ser Ser Lys Gly Tyr Asn Leu Phe Leu Val Ala Ala His Glu Phe  
 210 215 220  
 Gly His Ser Leu Gly Leu Asp His Ser Lys Asp Pro Gly Ala Leu Met  
 225 230 235 240  
 Phe Pro Ile Tyr Thr Tyr Thr Gly Lys Ser His Phe Met Leu Pro Asp  
 245 250 255  
 Asp Asp Val Gln Gly Ile Gln Ser Leu Tyr Gly Pro Gly Asp Glu Asp  
 260 265 270  
 Pro Asn Pro Lys His Pro Lys Thr Pro Asp Lys Cys Asp Pro Ser Leu  
 275 280 285  
 Ser Leu Asp Ala Ile Thr Ser Leu Arg Gly Glu Thr Met Ile Phe Lys  
 290 295 300  
 Asp Arg Phe Phe Trp Arg Leu His Pro Gln Gln Val Asp Ala Glu Leu  
 305 310 315 320  
 Phe Leu Thr Lys Ser Phe Trp Pro Glu Leu Pro Asn Arg Ile Asp Ala  
 325 330 335  
 Ala Tyr Glu His Pro Ser His Asp Leu Ile Phe Ile Phe Arg Gly Arg  
 340 345 350  
 Lys Phe Trp Ala Leu Asn Gly Tyr Asp Ile Leu Glu Gly Tyr Pro Lys  
 355 360 365  
 Lys Ile Ser Glu Leu Gly Leu Pro Lys Glu Val Lys Lys Ile Ser Ala  
 370 375 380  
 Ala Val His Phe Glu Asp Thr Gly Lys Thr Leu Leu Phe Ser Gly Asn  
 385 390 395 400  
 Gln Val Trp Arg Tyr Asp Asp Thr Asn His Ile Met Asp Lys Asp Tyr  
 405 410 415  
 Pro Arg Leu Ile Glu Glu Asp Phe Pro Gly Ile Gly Asp Lys Val Asp  
 420 425 430  
 Ala Val Tyr Glu Lys Asn Gly Tyr Ile Tyr Phe Phe Asn Gly Pro Ile  
 435 440 445  
 Gln Phe Glu Tyr Ser Ile Trp Ser Asn Arg Ile Val Arg Val Met Pro  
 450 455 460  
 Ala Asn Ser Ile Leu Trp Cys  
 465 470

&lt;210&gt; 33

&lt;211&gt; 183

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 33

Met Asp Pro Gly Thr Val Ala Thr Met Arg Lys Pro Arg Cys Ser Leu  
 1 5 10 15  
 Pro Asp Val Leu Gly Val Ala Gly Leu Val Arg Arg Arg Arg Tyr

```

      20      25      30
Ala Leu Ser Gly Ser Val Trp Lys Lys Arg Thr Leu Thr Trp Arg Val
      35      40      45
Arg Ser Phe Pro Gln Ser Ser Gln Leu Ser Gln Glu Thr Val Arg Val
      50      55      60
Leu Met Ser Tyr Ala Leu Met Ala Trp Gly Met Glu Ser Gly Leu Thr
      65      70      75      80
Phe His Glu Val Asp Ser Pro Gln Gly Gln Glu Pro Asp Ile Leu Ile
      85      90      95
Asp Phe Ala Arg Ala Phe His Gln Asp Ser Tyr Pro Phe Asp Gly Leu
      100      105      110
Gly Gly Thr Leu Ala His Ala Phe Phe Pro Gly Glu His Pro Ile Ser
      115      120      125
Gly Asp Thr His Phe Asp Asp Glu Glu Thr Trp Thr Phe Gly Ser Lys
      130      135      140
Ala Ser Gln Gln Leu Glu Gln Glu Leu Ala Gly Gly Ser Pro Val Asp
      145      150      155      160
Glu Glu Leu Gly Phe Ser Arg Gly Trp Arg Val Asn Pro Leu Gly Pro
      165      170      175
Gly Ser Pro Glu Arg Leu Ser
      180

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&lt;210&gt; 34

&lt;211&gt; 390

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 34

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Met Gly Arg Gly Ala Arg Val Pro Ser Glu Ala Pro Gly Ala Gly Val
  1      5      10      15
Glu Arg Arg Trp Leu Gly Ala Ala Leu Val Ala Leu Cys Leu Leu Pro
      20      25      30
Ala Leu Val Leu Leu Ala Arg Leu Gly Ala Pro Ala Val Pro Ala Trp
      35      40      45
Ser Ala Ala Gln Gly Asp Val Ala Ala Leu Gly Leu Ser Ala Val Pro
      50      55      60
Pro Thr Arg Val Pro Gly Pro Leu Ala Pro Arg Arg Arg Arg Tyr Thr
      65      70      75      80
Leu Thr Pro Ala Arg Leu Arg Trp Asp His Phe Asn Leu Thr Tyr Arg
      85      90      95
Ile Leu Ser Phe Pro Arg Asn Leu Leu Ser Pro Arg Glu Thr Arg Arg
      100      105      110
Ala Leu Ala Ala Ala Phe Arg Met Trp Ser Asp Val Ser Pro Phe Ser
      115      120      125
Phe Arg Glu Val Ala Pro Glu Gln Pro Ser Asp Leu Arg Ile Gly Phe
      130      135      140
Tyr Pro Ile Asn His Thr Asp Cys Leu Val Ser Ala Leu His His Cys
      145      150      155      160
Phe Asp Gly Pro Thr Gly Glu Leu Ala His Ala Phe Phe Pro Pro His
      165      170      175
Gly Gly Ile His Phe Asp Asp Ser Glu Tyr Trp Val Leu Gly Pro Thr
      180      185      190
Arg Tyr Ser Trp Lys Lys Gly Val Trp Leu Thr Asp Leu Val His Val
      195      200      205
Ala Ala His Glu Ile Gly His Ala Leu Gly Leu Met His Ser Gln His
      210      215      220
Gly Arg Ala Leu Met His Leu Asn Ala Thr Leu Arg Gly Trp Lys Ala
      225      230      235      240

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Leu Ser Gln Asp Glu Leu Trp Gly Leu His Arg Leu Tyr Gly Cys Leu  
 245 250 255  
 Asp Arg Leu Phe Val Cys Ala Ser Trp Ala Arg Arg Gly Phe Cys Asp  
 260 265 270  
 Ala Arg Arg Arg Leu Met Lys Arg Leu Cys Pro Ser Ser Cys Asp Phe  
 275 280 285  
 Cys Tyr Glu Phe Pro Phe Pro Thr Val Ala Thr Thr Pro Pro Pro Pro  
 290 295 300  
 Arg Thr Lys Thr Arg Leu Val Pro Glu Gly Arg Asn Val Thr Phe Arg  
 305 310 315 320  
 Cys Gly Gln Lys Ile Leu His Lys Lys Gly Lys Val Tyr Trp Tyr Lys  
 325 330 335  
 Asp Gln Glu Pro Leu Glu Phe Ser Tyr Pro Gly Tyr Leu Ala Leu Gly  
 340 345 350  
 Glu Ala His Leu Ser Ile Ile Ala Asn Ala Val Asn Glu Gly Thr Tyr  
 355 360 365  
 Thr Cys Val Val Arg Arg Gln Gln Arg Val Leu Thr Thr Tyr Ser Trp  
 370 375 380  
 Arg Val Arg Val Arg Gly  
 385 390

&lt;210&gt; 35

&lt;211&gt; 660

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 35

Met Glu Ala Leu Met Ala Arg Gly Ala Leu Thr Gly Pro Leu Arg Ala  
 1 5 10 15  
 Leu Cys Leu Leu Gly Cys Leu Leu Ser His Ala Ala Ala Ala Pro Ser  
 20 25 30  
 Pro Ile Ile Lys Phe Pro Gly Asp Val Ala Pro Lys Thr Asp Lys Glu  
 35 40 45  
 Leu Ala Val Gln Tyr Leu Asn Thr Phe Tyr Gly Cys Pro Lys Glu Ser  
 50 55 60  
 Cys Asn Leu Phe Val Leu Lys Asp Thr Leu Lys Lys Met Gln Lys Phe  
 65 70 75 80  
 Phe Gly Leu Pro Gln Thr Gly Asp Leu Asp Gln Asn Thr Ile Glu Thr  
 85 90 95  
 Met Arg Lys Pro Arg Cys Gly Asn Pro Asp Val Ala Asn Tyr Asn Phe  
 100 105 110  
 Phe Pro Arg Lys Pro Lys Trp Asp Lys Asn Gln Ile Thr Tyr Arg Ile  
 115 120 125  
 Ile Gly Tyr Thr Pro Asp Leu Asp Pro Glu Thr Val Asp Asp Ala Phe  
 130 135 140  
 Ala Arg Ala Phe Gln Val Trp Ser Asp Val Thr Pro Leu Arg Phe Ser  
 145 150 155 160  
 Arg Ile His Asp Gly Glu Ala Asp Ile Met Ile Asn Phe Gly Arg Trp  
 165 170 175  
 Glu His Gly Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala  
 180 185 190  
 His Ala Phe Ala Pro Gly Thr Gly Val Gly Gly Asp Ser His Phe Asp  
 195 200 205  
 Asp Asp Glu Leu Trp Thr Leu Gly Glu Gly Gln Val Val Arg Val Lys  
 210 215 220  
 Tyr Gly Asn Ala Asp Gly Glu Tyr Cys Lys Phe Pro Phe Leu Phe Asn  
 225 230 235 240  
 Gly Lys Glu Tyr Asn Ser Cys Thr Asp Thr Gly Arg Ser Asp Gly Phe

245 250 255  
 Leu Trp Cys Ser Thr Thr Tyr Asn Phe Glu Lys Asp Gly Lys Tyr Gly  
 260 265 270  
 Phe Cys Pro His Glu Ala Leu Phe Thr Met Gly Gly Asn Ala Glu Gly  
 275 280 285  
 Gln Pro Cys Lys Phe Pro Phe Arg Phe Gln Gly Thr Ser Tyr Asp Ser  
 290 295 300  
 Cys Thr Thr Glu Gly Arg Thr Asp Gly Tyr Arg Trp Cys Gly Thr Thr  
 305 310 315 320  
 Glu Asp Tyr Asp Arg Asp Lys Lys Tyr Gly Phe Cys Pro Glu Thr Ala  
 325 330 335  
 Met Ser Thr Val Gly Gly Asn Ser Glu Gly Ala Pro Cys Val Phe Pro  
 340 345 350  
 Phe Thr Phe Leu Gly Asn Lys Tyr Glu Ser Cys Thr Ser Ala Gly Arg  
 355 360 365  
 Ser Asp Gly Lys Met Trp Cys Ala Thr Thr Ala Asn Tyr Asp Asp Asp  
 370 375 380  
 Arg Lys Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val  
 385 390 395 400  
 Ala Ala His Glu Phe Gly His Ala Met Gly Leu Glu His Ser Gln Asp  
 405 410 415  
 Pro Gly Ala Leu Met Ala Pro Ile Tyr Thr Tyr Thr Lys Asn Phe Arg  
 420 425 430  
 Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Glu Leu Tyr Gly Ala Ser  
 435 440 445  
 Pro Asp Ile Asp Leu Gly Thr Gly Pro Thr Pro Thr Leu Gly Pro Val  
 450 455 460  
 Thr Pro Glu Ile Cys Lys Gln Asp Ile Val Phe Asp Gly Ile Ala Gln  
 465 470 475 480  
 Ile Arg Gly Glu Ile Phe Phe Phe Lys Asp Arg Phe Ile Trp Arg Thr  
 485 490 495  
 Val Thr Pro Arg Asp Lys Pro Met Gly Pro Leu Leu Val Ala Thr Phe  
 500 505 510  
 Trp Pro Glu Leu Pro Glu Lys Ile Asp Ala Val Tyr Glu Ala Pro Gln  
 515 520 525  
 Glu Glu Lys Ala Val Phe Phe Ala Gly Asn Glu Tyr Trp Ile Tyr Ser  
 530 535 540  
 Ala Ser Thr Leu Glu Arg Gly Tyr Pro Lys Pro Leu Thr Ser Leu Gly  
 545 550 555 560  
 Leu Pro Pro Asp Val Gln Arg Val Asp Ala Ala Phe Asn Trp Ser Lys  
 565 570 575  
 Asn Lys Lys Thr Tyr Ile Phe Ala Gly Asp Lys Phe Trp Arg Tyr Asn  
 580 585 590  
 Glu Val Lys Lys Lys Met Asp Pro Gly Phe Pro Lys Leu Ile Ala Asp  
 595 600 605  
 Ala Trp Asn Ala Ile Pro Asp Asn Leu Asp Ala Val Val Asp Leu Gln  
 610 615 620  
 Gly Gly Gly His Ser Tyr Phe Phe Lys Gly Ala Tyr Tyr Leu Lys Leu  
 625 630 635 640  
 Glu Asn Gln Ser Leu Lys Ser Val Lys Phe Gly Ser Ile Lys Ser Asp  
 645 650 655  
 Trp Leu Gly Cys  
 660

&lt;210&gt; 36

&lt;211&gt; 707

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

<400> 36  
 Met Ser Leu Trp Gln Pro Leu Val Leu Val Leu Val Leu Gly Cys  
 1 5 10 15  
 Cys Phe Ala Ala Pro Arg Gln Arg Gln Ser Thr Leu Val Leu Phe Pro  
 20 25 30  
 Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr  
 35 40 45  
 Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser  
 50 55 60  
 Lys Ser Leu Gly Pro Ala Leu Leu Leu Gln Lys Gln Leu Ser Leu  
 65 70 75 80  
 Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr  
 85 90 95  
 Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly  
 100 105 110  
 Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr  
 115 120 125  
 Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala  
 130 135 140  
 Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr  
 145 150 155 160  
 Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly  
 165 170 175  
 Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe  
 180 185 190  
 Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu  
 195 200 205  
 Leu Trp Ser Leu Gly Lys Gly Val Val Val Pro Thr Arg Phe Gly Asn  
 210 215 220  
 Ala Asp Gly Ala Ala Cys His Phe Pro Phe Ile Phe Glu Gly Arg Ser  
 225 230 235 240  
 Tyr Ser Ala Cys Thr Thr Asp Gly Arg Ser Asp Gly Leu Pro Trp Cys  
 245 250 255  
 Ser Thr Thr Ala Asn Tyr Asp Thr Asp Asp Arg Phe Gly Phe Cys Pro  
 260 265 270  
 Ser Glu Arg Leu Tyr Thr Arg Asp Gly Asn Ala Asp Gly Lys Pro Cys  
 275 280 285  
 Gln Phe Pro Phe Ile Phe Gln Gly Gln Ser Tyr Ser Ala Cys Thr Thr  
 290 295 300  
 Asp Gly Arg Ser Asp Gly Tyr Arg Trp Cys Ala Thr Thr Ala Asn Tyr  
 305 310 315 320  
 Asp Arg Asp Lys Leu Phe Gly Phe Cys Pro Thr Arg Ala Asp Ser Thr  
 325 330 335  
 Val Met Gly Gly Asn Ser Ala Gly Glu Leu Cys Val Phe Pro Phe Thr  
 340 345 350  
 Phe Leu Gly Lys Glu Tyr Ser Thr Cys Thr Ser Glu Gly Arg Gly Asp  
 355 360 365  
 Gly Arg Leu Trp Cys Ala Thr Thr Ser Asn Phe Asp Ser Asp Lys Lys  
 370 375 380  
 Trp Gly Phe Cys Pro Asp Gln Gly Tyr Ser Leu Phe Leu Val Ala Ala  
 385 390 395 400  
 His Glu Phe Gly His Ala Leu Gly Leu Asp His Ser Ser Val Pro Glu  
 405 410 415  
 Ala Leu Met Tyr Pro Met Tyr Arg Phe Thr Glu Gly Pro Pro Leu His  
 420 425 430  
 Lys Asp Asp Val Asn Gly Ile Arg His Leu Tyr Gly Pro Arg Pro Glu  
 435 440 445

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Pro Glu Pro Arg Pro Pro Thr Thr Thr Thr Pro Gln Pro Thr Ala Pro
  450                      455                      460
Pro Thr Val Cys Pro Thr Gly Pro Pro Thr Val His Pro Ser Glu Arg
  465                      470                      475                      480
Pro Thr Ala Gly Pro Thr Gly Pro Pro Ser Ala Gly Pro Thr Gly Pro
                      485                      490                      495
Pro Thr Ala Gly Pro Ser Thr Ala Thr Thr Val Pro Leu Ser Pro Val
                      500                      505                      510
Asp Asp Ala Cys Asn Val Asn Ile Phe Asp Ala Ile Ala Glu Ile Gly
  515                      520                      525
Asn Gln Leu Tyr Leu Phe Lys Asp Gly Lys Tyr Trp Arg Phe Ser Glu
  530                      535                      540
Gly Arg Gly Ser Arg Pro Gln Gly Pro Phe Leu Ile Ala Asp Lys Trp
  545                      550                      555                      560
Pro Ala Leu Pro Arg Lys Leu Asp Ser Val Phe Glu Glu Pro Leu Ser
                      565                      570                      575
Lys Lys Leu Phe Phe Phe Ser Gly Arg Gln Val Trp Val Tyr Thr Gly
  580                      585                      590
Ala Ser Val Leu Gly Pro Arg Arg Leu Asp Lys Leu Gly Leu Gly Ala
  595                      600                      605
Asp Val Ala Gln Val Thr Gly Ala Leu Arg Ser Gly Arg Gly Lys Met
  610                      615                      620
Leu Leu Phe Ser Gly Arg Arg Leu Trp Arg Phe Asp Val Lys Ala Gln
  625                      630                      635                      640
Met Val Asp Pro Arg Ser Ala Ser Glu Val Asp Arg Met Phe Pro Gly
                      645                      650                      655
Val Pro Leu Asp Thr His Asp Val Phe Gln Tyr Arg Glu Lys Ala Tyr
  660                      665                      670
Phe Cys Gln Asp Arg Phe Tyr Trp Arg Val Ser Ser Arg Ser Glu Leu
  675                      680                      685
Asn Gln Val Asp Gln Val Gly Tyr Val Thr Tyr Asp Ile Leu Gln Cys
  690                      695                      700
Pro Glu Asp
705

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```

<210> 37
<211> 16
<212> PRT
<213> Homo sapiens

```

```

<220>
<221> VARIANT
<222> (3)...(5)
<223> Xaa = any amino acid

```

```

<221> VARIANT
<222> (7)...(7)
<223> Xaa = any amino acid

```

```

<221> VARIANT
<222> (11)...(12)
<223> Xaa = any amino acid

```

```

<221> VARIANT
<222> (13)...(13)
<223> Xaa = Glycine or Alanine

```

```

<400> 37

```



His Gly Xaa Xaa Xaa Pro Xaa Phe Asp Gly Xaa Xaa Xaa His Ala Phe  
1 5 10 15